Review

Quarter-Century Explorations of Bioactive Polyphenols: Diverse Health Benefits

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Abstract

Polyphenols, members of phytochemical superfamily rich in vegetables and fruits, include flavonoids, non-flavonoids, and phenolic acids. Their biological effects includes classical antioxidation (e.g., radical-scavenging, metal chelating, NOX inhibition, attenuation on mitochondrial respiration, inhibition on xanthine oxidase, and upregulations on endogenous antioxidant enzymes), multiple regulations on cell signaling (e.g., AMPK activation, SirT1 activation, eNOS activation, FOXO activation, NFκB inactivation, PI3K/AkT inhibition, mTORC1 inhibition, PKC inhibition, MAPK inhibition, ERK inhibition, JAK/STAT inhibition, IKK/JNK inhibition, PDE inhibition, β-catenin inactivation, downregulation on TLR expression, ACE inhibition, adiponectin elevation, attenuated ET-1 production, and K$^+$ channel activation), and many other actions (e.g., inhibition on α-glucosidase, anticoagulation, γ-secretase inhibition, monoamine oxidase inhibition, LPL upregulation, ANGPTL4 suppression, upregulation on paraoxonase 1, PAI-1 downregulation, tPA upregulation, immunoregulation, epigenetic modulation, and altered gut microbiota). Such multi- targeting and functions exhibiting antioxidative stress and antiinflammation as major pillars along with many other antagonisms could not only afford healthy polyphenols suitable supplements for promoting health, but also advance them to therapeutic applications. This review aims to translate diverse polyphenolic biochemical actions to clinical applications in fighting against non-communicable diseases such as CVD, cancer, diabetes, obesity, neurodegeneration, inflammatory diseases (e.g., IBD, IBS, NAFLD, *etc.*), AMD, allergy, and autoimmunity as well as communicable infection (e.g., bacteria, fungal, and viral).

Keywords: polyphenol; AMPK; antioxidation; ROS; CVD; cancer; diabetes; obesity; inflammation; infection; immunoregulation; neurodegeneration; communicable; non-communicable; PI3K; mTOR; NFκB

1. Introduction

Plants coexist with human beings on this planet, in part replenishing some oxygen through photosynthesis. Plant products: vegetables and fruits supply us with micronutrients (e.g., vitamins) and macronutrients including carbohydrates, proteins, and fats for daily lives. Plants also play "middleman" roles in delivering minerals to human (a few examples: as micronutrients for physiological functions (e.g., ion channels), as catalytic metals in active centers for proper biologically enzymatic reactions, and as electrolytes for intra/extra- cellular fluid balance/osmosis).

The phytochemical superfamily consisting of nitrogen-containing alkaloids (e.g., caffeine, morphine, nicotine, quinine, codeine, cocaine, capsaicin, *etc.*), polyphenols (e.g., flavonoids, non-flavonoids, iso/flavanones, phenolic acids, *etc.*), and terpenoids/isoprenoids (e.g., saponins, lycopene, paclitaxel, *etc.*) is plant secondary metabolites responsible for plant pigments, structures, and functions (e.g., chemical defense, pollinator attraction, and environmental adaptation (e.g., UV protection)). Nearly 80% of these secondary metabolites are made by higher plants. The superfamily is unique in supporting plant survival and growth; these compounds also provide human balanced and healthy nutrients.

Other phytochemcials such as steroids, essential fatty acids, vitamins, and many other critical molecules are also pivotal to human lives. For instance, Vitamin A/B/C/D/E are vital to physiological functions. α-Linolenic acid (n-3 C18:3) and linoleic acid (n-6 C18:2) known as vitamin F are precursors for biosynthesis of long-chain polyunsaturated fatty acids (e.g., EPA, n-3 C20:5; DHA, n-3 C22:6) and arachidonic acid (n-6 C20:4), respectively, that are essential for human development. Linoleic acid is also an important component in building skin water barrier interacting with ceramide. Phytosterols (e.g., β-sitosterol) compete with animal cholesterol absorption in the small intestines. Phytoestrogens (e.g., genistein) are analogs to estrogen without estrogen harmful effects.

Polyphenols abundant in a wide variety of vegetables and fruits are historically known as antioxidants. The polyphenolic antioxidant contents (e.g., quercetin, caffeic acid, epicatechin) could somewhat provide scientific insights into a myth & fiction type of old saying "an apple a day keeps the doctor away" along with many other highly nutritious ingredients in apples. Furthermore, the French paradox could certainly underscore the powerful polyphenolic antioxidant resveratrol in cardioprotection.

This translational review, if not exclusively, highlights polyphenolic multi- targeting and functions in promoting human health and fighting against non-communicable (metabolic syndromes: CVD, diabetes, obesity, NAFLD; cancer; neurodegeneration; autoimmune; allergy; anemia; AMD; *etc*.) and communicable (viral infection) diseases. The anti-oxidative stress and anti-inflammatory effects as two major pillars plus diverse regulations on cell signaling and functions confer a broad spectrum of health benefits. The healthy polyphenols could become suitable daily supplements in the upcoming era of nutraceutics.

2. Biochemistry of Polyphenols

2.1 Chemical Structure

As indicated by the name, bioactive polyphenols are multiple-hydroxyl (-OH) aromatic phenolic phytochemicals. The complex polyphenols typically include three categories: flavonoids, non-flavonoids, and phenolic acids. (a) Flavonoids can be subdivided into six sub-classes: (*i*) flavonols (e.g., quercetin, kaempferol, myricetin, isorhamnetin); (*ii*) flavones (e.g., luteolin, apigenin); (*iii*) isoflavones (e.g., daidzein, genistein); (*iv*) flavanones (e.g., naringenin, hesperetin); (*v*) flavanols (e.g., catechins, epicatechin (EC), gallocatechin (GC), and epigallocatechin (EGC) and their gallates (EGCG)), and (*vi*) anthocyanidins (e.g., malvidin, cyanidin). Proanthocyanidins are traditionally considered to be condensed tannins. (b) Non-flavonoids are further classified into three subgroups (stilbenoids, lignans, and diarylheptanoids) that include resveratrol, curcumin, and coumarin as common examples. (c) In the category of phenolic acids, they include ellagic acid, tannic acid, gallic acid, and caffeic acid as well as many others (ferulic acid, syringic acid, sinapinic acid, *etc*.). Fig. 1 shows common typical polyphenols in the three categories.

2.2 Occurrence

Polyphenols are ubiquitously existing and abundant in plants (vegetables and fruits). (a) In the category of flavonoids, (*i*) catechins are found in green and white tea, grapes, cocoa, lentils, berries, artichoke, celery, *etc*.; (*ii*) iso/flavanones (e.g., naringenin, genistein, hesperetin) are found in oranges, grapefruit, lemon, *etc*.; flavanone genistein, a phytoestrogen, is rich in soybean; (*iii*) flavanols (e.g., kaempferol, quercetin, myricetin, isorhamnetin) are found in green vegetables, apples, berries, onions, chocolates, tea, red wine, *etc*.; (*iv*) quercetin is rich in fruits (cherries, apples), vegetables (curly kale, *Ginkgo biloba*, broccoli, red onion, lettuce), olive oil, tea, nuts, red wine, *etc*.; (*v*) anthocyanins are found in berries, red grapes, red wine, *etc*., while proanthocyanidins are traditionally considered to be condensed tannins; (*vi*) anthocyanidins (plant pigments; the sugar-free counterparts of anthocyanins) and their derivatives can be found in pomegranate, blueberries, raspberries,

cranberries, rice, corn, cherries, *etc*. (b) In non-flavonoids, (*i*) resveratrol is mainly found in white hellebore, polygonum cupsidatun, cranberries, grape skin, red wine, nut, *etc*., (*ii*) curcumin is rich in turmeric plants, mustard, and (*iii*) coumarin is abundant in licorice, strawberries, apricots, cherries, cinnamon, *etc*. (c) In the category of phenolic acids, (*i*) ellagic acid is found in walnuts, strawberries, pomegranates, cranberries, blackberries, guava, or grapes, (*ii*) tannic acid is in nettles, tea, or berries, (*iii*) gallic acid is found in tea leaves, mango, cranberries, strawberries, oak bark, gallnuts, sumac witch hazel rhubarb, soy, gallnuts, sumac witch hazel, *etc*., and (*iv*) caffeic acid widely exists in coffee, spearmint, oregano, rosemary, sage, peppermint, bark, freshwater fern, mushroom, blueberries, kiwis, plums, cherries, apples, *etc*.

2.3 Metabolism

Polyphenol oxidase (PPO) also known as tyrosinase is responsible for polyphenol metabolism/oxidation in plants. The copper-containing enzyme typically catalyzes two different reactions in the presence of molecular oxygen: the hydroxylation of monophenols to ortho-diphenol and the oxidation of *o*-diphenol to *o*-quinone, which accounts for darkening/browning of agricultural products affecting shelf-lives. The oxidation could infer the ability of polyphenols to sequester free radicals deriving from interaction with oxygen.

Ascorbic acid, citric acid, glutathione, cinnamic acid, cysteine, glycine, phytic acid, salicylic acid, unsaturated fatty acids, isothiocyanate, β-cyclodextrin, NaCl, cold, high pressure CO_2, hydroxylated naphthylchalcone, α/β naphthol, UV-C (254 nm), γ-radiation, *etc*. inhibit PPO [1,2], suppressing fruit/vegetable discoloration of black, brown, red, green, *etc*. Interestingly, polyphenols (e.g., flavonoids, phenolic acid, curcumin, quercetin, *etc*.) *per se* are effective inhibitors for PPO, undergoing substrate inhibition and quenching PPO activity by their $Cu2^+$-chelating capacities resulting from the hydroxyl group(s) in combination with the A and B rings in flavones and flavonols, for instance. Such relevance reinforces the notion that polyphenols are powerful antioxidants.

2.4 Possible Polyphenol Receptor

Limited research remaining elusive is available concerning polyphenol receptor(s); thus far, 67-kDa laminin receptor functions as a cell-surface EGCG receptor and EGCG is able to activate this laminin receptor signaling [3,4]. It is possible that polyphenol affects a wide range of cell functions through simple diffusion or membrane lipid raft. Some polyphenols are lipophilic; membrane lipid portioning could involve its entry or reception.

3. Mode of Polyphenolic Actions

In addition to classical antioxidation and antiinflammation as major pillars, multiply targeting signal-
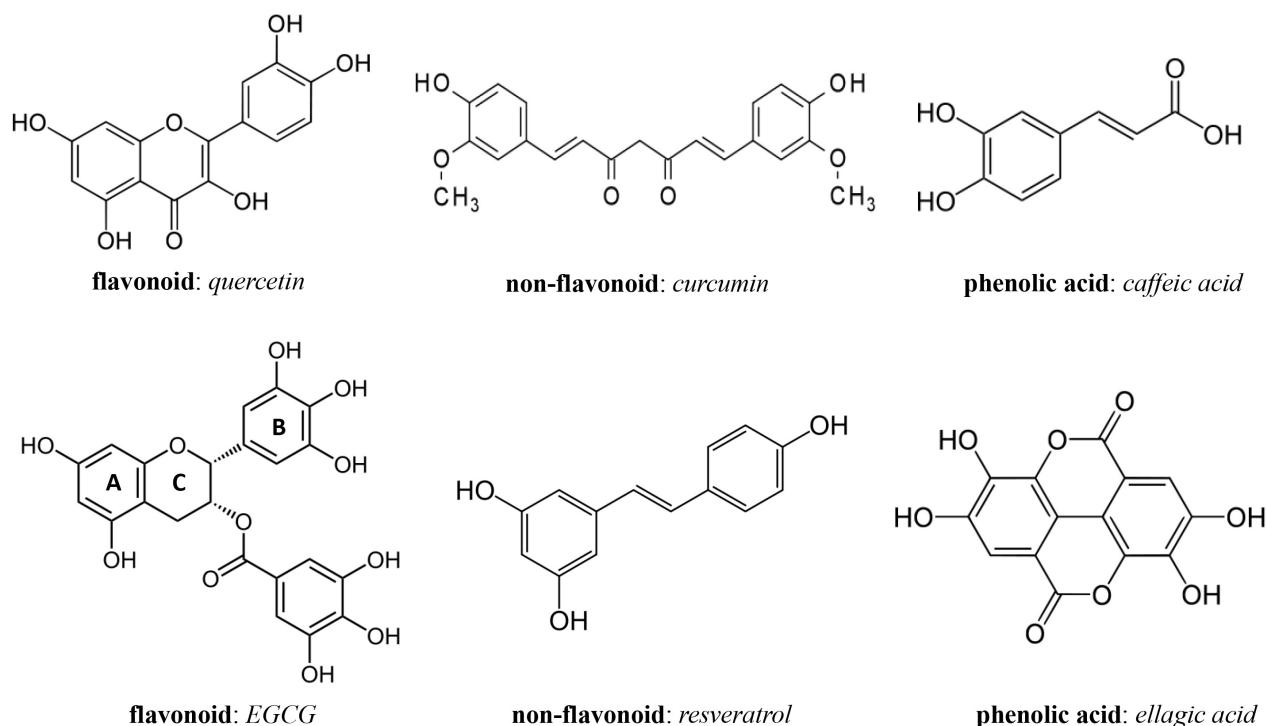
Fig. 1. Chemical structures of polyphenols. Typical examples of polyphenols are shown in three major categories as flavonoids, non-flavonoids, and phenolic acids.

ing enzymes and corresponding pathways (Fig. 2) makes polyphenol diversely functional in health promotion and disease prevention and antagonism [5].

3.1 Antioxidation

The structural signatures afford radical scavenging as well as metal chelating, arresting free radical chain reaction of biological damages. Polyphenols are also able to inhibit reactive oxygen species (ROS) production from mitochondrial respiration, respiratory burst, and xanthine oxidase. Their antioxidant potentials are further enhanced by upregulations on endogenous antioxidant enzymes that are responsible for ROS detoxification.

(1) Radical-scavenging. The structural features of poly hydroxyl groups on aromatic (phenyl) ring(s) make polyphenolic compounds much easier undertaking oxidation, exhibiting radical-scavenging of OH• and NO•. Some hydroxyl(s) depending on the adjacent chemical groups (e.g., methoxy) or positions (e.g., ortho) are even more potent for radical-scavenging activity. For instance, the orthomethoxy group in curcumin can form an intramolecular hydrogen bond with the phenolic hydrogen, making the H-atom abstraction from the orthomethoxyphenols. The H abstraction from these groups is responsible for the remarkable antioxidant activity. The trihydroxyl group on the B ring and the gallate moiety esterified at the 3′ position in the C ring of EGCG are believed to contribute to its scavenging activity.

(2) Metal chelating. Polyphenols quench the Fenton reaction to attenuate oxidative stress. In the classical Fenton reactions, transition metal: $Fe2^+$, $Cu2^+$, $Co2^+$, $Ti3^+$, $Cr5^+$, or $V2^+$ readily drives OH• formation from H_2O_2 [6,7]. Curcumin binds and chelates transition metal ($Cu2^+$ and $Fe2^+$) ions. Similarly, EGCG chelates $Fe2^+$ for inhibiting $Fe2^+$-induced DNA break.

(3) NOX inhibition. Resveratrol [8,9], curcumin [8], apocynin [10], and many other polyphenols are able to inhibit NOX. For instance, curcumin [9] decreases NOX subunit (e.g., p67phox, p22phox, and gp91phox) expression, while resveratrol suppresses p47phox expression, both of which attenuate the generation of $O_2•^-$ during innate responses to infection.

(4) Attenuation on mitochondrial respiration. By blocking the respiratory chain and ATPase at the inner mitochondrial membrane [11], polyphenols (nonflavonoid resveratrol, flavonoids (theaflavins: catechin, epicatechins, and epigallocatechin, *etc*.), flavanol quercitrin, iso/flavanones (e.g., genistein), *etc*.) thus inhibit mitochondrial ATP synthesis, attenuating mitochondrial ROS production such as H_2O_2 and $O_2•^-$.

(5) Inhibition on xanthine oxidase. Polyphenols (e.g., resveratrol analogs [12], curcumin [13], EGCG [14], phenolic acids [15], capsaicin [16], quercetins [17], anthocyanins [17],) all inhibit xanthine oxidase, a ROS producing enzyme.
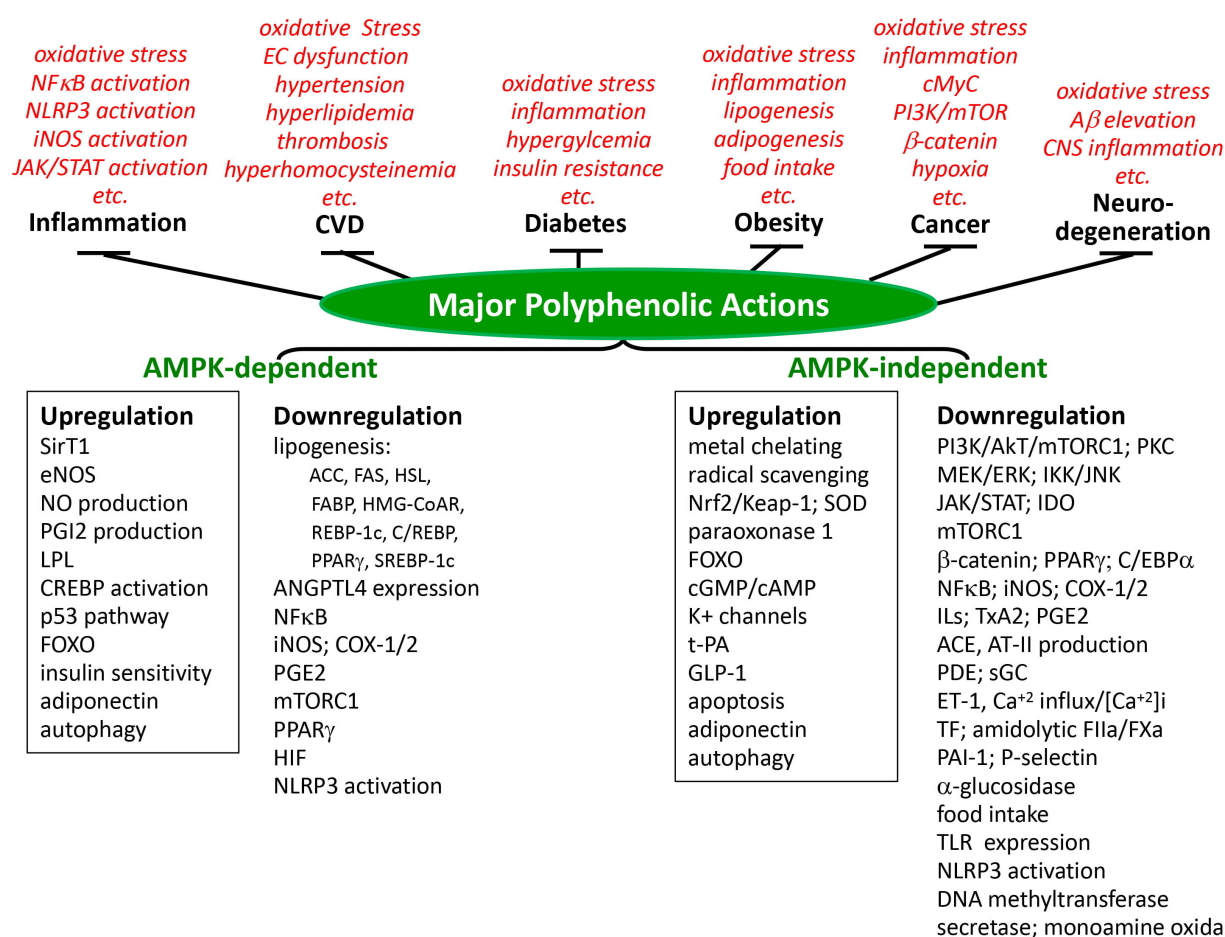
oxidative stress
NFκB activation
NLRP3 activation
iNOS activation
JAK/STAT activation
etc.

oxidative Stress
EC dysfunction
hypertension
hyperlipidemia
thrombosis
hyperhomocysteinemia
etc.

oxidative stress
inflammation
hypergylcemia
insulin resistance
etc.

oxidative stress
inflammation
lipogenesis
adipogenesis
food intake
etc.

oxidative stress
inflammation
cMyC
PI3K/mTOR
β-catenin
hypoxia
etc.

oxidative stress
Aβ elevation
CNS inflammation
etc.

Inflammation   **CVD**   **Diabetes**   **Obesity**   **Cancer**   **Neuro-degeneration**

Major Polyphenolic Actions

AMPK-dependent

Upregulation
SirT1
eNOS
NO production
PGI2 production
LPL
CREBP activation
p53 pathway
FOXO
insulin sensitivity
adiponectin
autophagy

Downregulation
lipogenesis:
  ACC, FAS, HSL,
  FABP, HMG-CoAR,
  REBP-1c, C/REBP,
  PPARγ, SREBP-1c
ANGPTL4 expression
NFκB
iNOS; COX-1/2
PGE2
mTORC1
PPARγ
HIF
NLRP3 activation

AMPK-independent

Upregulation
metal chelating
radical scavenging
Nrf2/Keap-1; SOD
paraoxonase 1
FOXO
cGMP/cAMP
K+ channels
t-PA
GLP-1
apoptosis
adiponectin
autophagy

Downregulation
PI3K/AkT/mTORC1; PKC
MEK/ERK; IKK/JNK
JAK/STAT; IDO
mTORC1
β-catenin; PPARγ; C/EBPα
NFκB; iNOS; COX-1/2
ILs; TxA2; PGE2
ACE, AT-II production
PDE; sGC
ET-1, Ca^{+2} influx/[Ca^{+2}]i
TF; amidolytic FIIa/FXa
PAI-1; P-selectin
α-glucosidase
food intake
TLR expression
NLRP3 activation
DNA methyltransferase
secretase; monoamine oxidase

Fig. 2. Biochemical mechanisms of polyphenolic actions in fighting diseases. Diverse AMPK- dependent/independent up and down - regulations (lower panel shown in black; refer to the texts for details) readily multiply target and antagonize against diseases' pathogeneses or risks (upper panel shown as red italic). Please also refer to the text for individual actions that target disease manifestations.

(6) *Upregulations on endogenous antioxidant enzymes. In vivo*, ROS detoxification by curcumin may be mediated through antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase (Px), which is believed to be mediated by nuclear factor erythroid 2-related factor 2 (Nrf2) and FOXO activations and target antioxidant gene expression. (a) Nrf2 is a conserved master regulator of cellular antioxidant responses [18,19]. Polyphenols (e.g., resveratrol, curcumin, EGCG, *etc.*) activate Nrf2 by possible phosphorylation at S40 for its nuclear translocation. Upon binding to antioxidant response element of target genes, phytochemicals promote antioxidant enzyme (catalase, GR, GSHPx, GSHT, heme oxygenase (HO)-1, and SOD) expression. For instance, curcumin induces Nrf2 and increases the target gene HO-1 expression also favoring apoptosis with anti-tumor action. (b) As a Michael acceptor, curcumin readily reacts with GSH (γ-L-glutamyl-L-cysteinylglycine, the main non-protein thiol found in cells) and thioredoxin. Similarly, resveratrol stimulates endogenous antioxidant enzymes MnSOD and catalase and antioxidant gene (e.g.,

NQO-1 and GST-P1) expression, while EGCG increases SOD and GSH-Px activities with increased cellular GSH.

3.2 AMPK-Dependent Mechanism

Polyphenols (e.g., catechin, curcumin, resveratrol, luteolin, corilagin, EGCG, EC, EGC, *etc.*) generally inhibit mitochondrial ATP synthesis to trigger AMPK activation, involving divergent downstream signaling cascades such as SirT1 activation, eNOS induction, anti-inflammatory relevance (e.g., NFκB, COX, and iNOS inhibitions), FOXO upregulation, promoting p53 pathway, LPL upregulation and suppressed ANGPTL4 mRNA expression, CREBP activation, mTORC1 inhibition, SREBP-1c inactivation, PPARγ inactivation, HIF-1α repression, adiponectin elevation, and autophagy activation. In addition, AMPK activation shifts MΦ M1 to M2 polarization. Anti-inflammatory M2 MΦs (as well as Treg) feature Th2 responses, resolving Th1 inflammation, immune tolerance, and profibrotic actions (tissue repair and remodeling) with high efferocytosis.

(7) *AMPK activation*. (a) The majority of polyphenols (e.g., catechin, curcumin, resveratrol, luteolin, rutin, corila-

gin, EGCG, EC, EGC, *etc.*) inhibit mitochondrial ATP synthesis by blocking the respiratory chain and ATPase at the inner mitochondrial membrane, thus activating AMPK. (*i*) Metabolically, AMPK activation mediates hypolipidemic effects including suppressed lipogenic transcription factors (e.g., SREBP1/2, C/REBP, *etc.*) and enzymes (e.g., HMG-CoA reductase, acetyl-CoA carboxylase, *etc.*) for *de novo* biosyntheses of cholesterol and fatty acids and TG formation. AMPK-mediated phosphorylation of the transcription factors and lipogenic enzymes inactivates activities. (*ii*) Concerning cell signaling, AMPK activation leads to SirT1 and FOXO activation as well as mTOR inhibition. (*iii*) AMPK activation could also shift MΦ M1 to M2 polarization; anti-inflammatory M2 MΦs (as well as Treg) feature Th2 responses, resolving Th1 inflammation, immune tolerance, and profibrotic actions (tissue repair and remodeling) with high efferocytosis. (b) Additionally, resveratrol [20] inhibits cAMP-degrading PDEs (e.g., PDE4), resulting in accumulated cAMP that activates Epac1 for in turn stimulating PLCε. The resulting phosphorylated ryanodine receptor 2 triggers Ca^{2+} channel releasing Ca^{2+} from ER. The activated CamKKβ then phosphorylates and activates AMPK.

(*8*) *SirT1 activation.* SirT1 activation [20,21] triggers diverse signaling including AMPK activation, NFκB inactivation, eNOS activation, p53 activation, tumor suppressor FOXO upregulation for antioxidant enzyme (Mn-SOD) expression, early Treg differentiation (antiinflammation), suppressed lipogenesis (PPARγ inactivation) [22], longevity, *etc*. Resveratrol triggers an array of signal cascade to exhibit metabolic benefits via elevated NAD^+ and enhanced SirT1 activity, called AMPK-SirT1-PPARγ coactivator 1α (PGC-1α) axis. While phosporylating PGC-1α, AMPK increases NAD^+ levels and activates SirT1 that deacetylates PGC-1α. Thus, metabolic benefits such as anti-aging, anti-diabetic, and increases in FA oxidation, gluconeogenesis, and mitochondrial biogenesis and functions could result from indirectly activated SirT1 via competitive inhibition of cAMP-phosphodiesterases (PDE4) by polyphenol in red wine [20,21]. In these regards, resveratrol mimics caloric restriction, exercise, or short-term fasting in favoring longevity.

(*9*) *FOXO activation.* FOXO upregulation is largely a result of PI3K/AkT inhibition and AMPK/SirT1 activation [22], which mediates NFκB inactivation, HIF repression, antioxidant enzyme expression, and Treg differentiation. For further cancer protection, FOXO activation extends its effects to proapoptosis and antagonism against onco- gene/protein c-MyC; FOXO functions as a suppressive oncogene.

(*10*) *eNOS activation.* AMPK phosphorylates and activates eNOS; NO is considered anti-inflammatory. In addition, polyphenols such as resveratrol via such eNOS activation show benefits to insulin sensitivity and anti-hypertension. The resulting NO production activates

sGC for cGMP generation. Such eNOS activation mediates Glut4 translocation and increased glucose uptake/utilization by muscle cells [23,24], mimicking insulin action. In an EC-dependent vasodilation, resveratrol activates eNOS activity, NO production, GC activation, and subsequent cGMP production in addition to its ability to function as a non-selective PDE inhibitor. Taken together, resveratrol leads to cGMP accumulation and $Ca2^+$ effluxes for vascular dilation [25,26].

(*11*) *NFκB, COX, iNOS inhibitions.* (a) AMPK downregulates hallmark inflammatory transcription factor: NFκB [27] by at least two mechanisms. (*i*) AMPK increases NAD^+ for its consequent SirT1 activation. SirT1 deacetylates and activates PGC-1β while deacetylating and inactivating NFκB p65, an inflammatory master transcription factor. (*ii*) AMPK directly inactivates NFκB via mTORC1 inhibition (also see below section on mTORC1 inhibition); IκB kinase (IKK) phosphorylation by mTORC1 results in NFκB nuclear translocation and its transcriptional activity. NFκB is recognized as a hallmark of inflammation. (b) In addition to proinflammatory (TNF, IL-1, IL-6) genes, COX-2 and iNOS are important gene targets of NFκB [27]. Therefore, inflammatory TNF, IL1/6, PGE2, and NO production are all suppressed by polyphenols. For instance, curcumin attenuates proinflammatory cytokine (e.g., IL-1β, IL-6, and TNF-α) expression and inhibits STAT3 phosphorylation and activation. In a similar manner, curcumin downregulates AP-1 and cytokine (IL-1α and TNF-α) expression. Importantly, NFκB is involved in cell proliferation and tumor cell survival, linking inflammation and cancer; thus, NFκB inactivation bears anti-cancer action [27].

(*12*) *Promoting p53 pathway.* Mediated by AMPK activation, curcumin is able to phosphorylate at S15 in p53 N-terminus [28–33], which attenuates p53 interaction with its negative regulator MDM2 for promoting p53 stabilization and nuclear translocation for its transcriptional activity. Such action favors cell apoptosis and suppresses cell proliferation. (a) p53 inhibits Bcl-2, while enhancing the intrinsic apoptotic pathway including elevated cytoplasmic proapototic proteins (PIDD, Bid) and mitochondrial proapoptotic proteins: Bax, Bak, Puma, and Noxa. (b) p53 also promotes the extrinsic pathway by elevating death receptors (Fas/Apo1, DR 5, *etc.*).

(*13*) *LPL upregulation.* AMPK phosphorylates and activates LPL [33], a major circulating enzyme responsible for TG-rich lipoprotein catabolism and TG degradation in lowering blood TG level.

(*14*) *CREBP activation and BDNF expression.* Mediated by AMPK activation, polyphenols (e.g., curcumin, EGCG) phosphorylate CREBP that in turn activates brain derived neurotrophic factor (BDNF) expression. BDNF is required for long term potential and cognition process in hippocampus [31,32].

(*15*) *mTORC1 inhibition*. There are at least two mechanisms by which AMPK inhibits mTORC1. (a) AMPK phosphorylates and activates TSC2, a negative upstream regulator of mTORC1 [34–37]. (b) Alternatively, AMPK directly phosphorylates and inactivates raptor, an adaptor protein in mTORC1 complex. Both actions ensure mTORC1 inhibition by AMPK activation. mTORC1 is responsible for upregulating PPARγ, SREBP-1c, HIF, inflammation (IKK phosphorylation and NFκB activation), and cell proliferation/differentiation/survival while downregulating autophagy. Accordingly, AMPK-dependent mTORC1 inhibition results in downregulations on PPARγ, SREBP-1c, and HIF, which has been reported to be beneficial to aging related pathological conditions such as cognition decline, Alzheimer's (AD), cancer, and kidney, heart, and autoimmune diseases over the past 40 years.

mTORC1 inhibition presents HIF repression and NFκB inactivation. mTORC1 activation, otherwise, promotes glycolysis via upregulation of HIF1α and c-Myc (tumorigenesis); stimulates lipid biosynthesis and the pentose phosphate pathway through sterol regulatory element binding protein 1 (SREBP-1) (lipogenesis) [38]; and positively controls glutamine metabolism by SIRT4 repression. Curcumin, resveratrol, EGCG, genistein, and caffeine readily inhibit both mTORC1 and mTORC2 [39], which is a consequence of AMPK activation and/or PI3K/AkT inhibition.

(*16*) *SREBP inactivation*. mTORC1 inhibition in turn inactivates SREBP-1c, resulting in suppressed lipogenesis including fatty acid synthesis (e.g., acetyl-CoA carboxylase) and TG formation (lipin 1) [37], characteristics of fat accumulation in obesity. mTORC1 is responsible for SREBP-1c phosphorylation, cleavage, and its enhanced nuclear translocation and transcriptional activity.

(*17*) *PPARγ inactivation*. As the result of mTORC1 inhibition and SirT1 activation [40] by phytochemicals via AMPK activation, PPARγ translation and transcriptional activity are significantly suppressed. PPARγ is a known master gene for adipogenesis and adipocyte differentiation [37,40]; PPARγ inactivation thus blocks adipogenesis, lipogenesis, and fat accumulation, contributing to antiobesity.

(*18*) *HIF-1α repression*. mTORC1 inhibition downregulates the expression of HIF-1α [34–36], contributing to antiinflammation and tumor suppression. HIF-1α is an inflammatory as well as angiogenic transcription factor. (a) As an inflammatory trigger, hypoxia (HIFα) promotes Th17 expansion and IL-17 production while promoting degradation of Treg FOXp3 through VHL E3 ligase. (b) As an angiogenic factor, HIFα targets many genes including VEGF for cancer progression, metastasis, and cancer stem cell expansion.

(*19*) *Suppressed ANGPTL4 expression*. Upon AMPK-dependent downregulation on SREBP-1c, PPARγ, and HIFα, ANGPTL4 expression is suppressed. ANGPTL4, a target gene of SREBP-1c, is a negative regulator of LPL. ANGPTL4 expression could also be regulated by PPARγ, HIFα, and glucocordioid receptor; for instance, ANGPTL4 is induced by fasting and hypoxia. Thus, its repression facilitates LPL activity for TG degradation and hypoTG action.

(*20*) *Autophagy upregulation*. AMPK-dependent mTORC1 inhibition is able to upregulate autophagy. mTORC1 negatively regulates a complex consisting of essential autophagic proteins (e.g., ULK1, ATG13, ATG101, and FIP200). Alternatively independent of mTORC1 inhibition, direct PI3K/AkT inhibition could block phosphorylation of a crucial autophagic element: Beclin 1 that otherwise dimerizes and recruits 14-3-3 further being sequestered to cytoskeletal actin vimentin and intermediate filament complex. As a result of such blockage mediated by PI3K/AkT inhibition, autophagosome assembly is able to initiate autophagy.

Essentially, autophagy, an intracellular cleaning system including aggrephagy, xenophagy, mitophagy, and lipophagy, contributes to regenerating metabolic precursors, and cellular and tissue homeostasis by degrading long-lived proteins, protein aggregates, and defective organelles (e.g., mitochondria, ER, or peroxisomes), and cleaning subcellular debris.

Autophagy downregulates oxidation and prevents inflammation (e.g., NLRP3 inflammasome activation). (a) Mitophagy limits NLRP3 activation by removing damaged mitochondria. (b) Autophagosomal Atg16L1 readily inhibits ROS production; ROS is essential for NLRP3 activation (refer to as oxidation-inflammation axis). (c) Autophagy *per se* promotes lysosome (NLRP3 inflammasome) degradation through ubiquitination involving autophagosomal components p62 and LC3. (d) Furthermore, removal of pro-IL1β/18 by autophagy for NLRP3-mediated caspase 1 cleavage ensures antiiflammation. Thus, autophagy protects from inflammasome (NLRP3) activation that is essential for IL-1β/18 maturation and secretion. (e) Autophagy also plays role(s) in anti-viral (e.g., HIV), anti-bacteria (*Mtb*, *Shigella flexneri*), *etc*. (f) Limited information is available directly regarding autophagy upregulation in relation to cardioprotection. Apparently, resveratrol induces autophagy and thus possibly protects from MI.

(*21*) *Adiponectin elevation and signaling*. Increased adiponectin is reported in response to resveratrol that also upregulates the expression of adiponectin receptor-1. Resveratrol promotes the posttranslational multimerization and stability of adiponectin by DsbA-L that is induced upon AMPK activation and AkT-mediated FOXO1 activation [41]. (a) Adiponectin in contrast to its counterparts (e.g., leptin) is of antiinflammation in nature. For instance, circulating adiponectin appreciably declines in obese. Adiponectin attenuates TNF-α and IL-6 production while inducing expression of anti-inflammatory cytokines (e.g., IL-10 and IL-1 receptor antagonist). (b) Adponectin signaling generally triggers S-1-P formation

and AMP, PPARα, and p38 MAPK activation. (c) Its major metabolic functions include glucose homeostasis, insulin-sensitizing action, increased fatty acid oxidation, and downregulated hepatic gluconeogenesis, all of which fight against metabolic symptoms.

In a clinical trial [42], grape resveratrol increases serum adiponectin and downregulates inflammatory genes (*PAI-1, IL-6, AP-1, JUN, CREBP, etc.*). In an animal model [43], 7-O-galloyl-D-sedoheptulose increases adiponectin level while downregulating leptin, insulin, C-peptide, resistin, TNFα, and IL-6 in serum and proinflammatory NFκB p65, COX-2, iNOS, JNK, phospho-JNK, AP-1, TGFβ1, and fibronectin.

3.3 AMPK-Independent Mechanisms

By inhibiting multiple signaling enzymes or enzymes *per se*, polyphenols downregulate corresponding signaling pathways and suppress metabolic activities, respectively.

A wide-range of AMPK-independent actions [44] include PI3K/AkT inhibition, direct mTORC1 inhibition, β-catenin inactivation, FOXO activation, PDE inhibition, ACE inhibition, attenuated ET-1 expression, proapoptosis, JNK or IKK inhibition, Nrf2 activation, Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inactivation, PKC inhibition, and MAPK inactivation. In addition, many polyphenolic effects concern non-signaling related enzyme inhibitions including secretase inhibition, monoamine oxidase inhibition, α-glucosidase inhibition, anticoagulation, and anti-thrombosis.

(*22*) *PI3K/AkT inhibition.* Polyphenols generally inhibit PI3K/AkT signaling cascade; its downstream effects include IKK inhibition and FOXO activation, exhibiting antiinflammation. Synergistically with AMPK activation, PI3K/AkT inhibition leads to mTORC1 inhibition. Thus, PI3K/AkT inhibition exhibits a broad spectrum of events including NFκB inactivation, FOXO upregulation, HIF repression, *etc*.

(*23*) *β-catenin inactivation.* By inhibiting PI3K/AkT, curcumin blocks axin/APC/GSK3β/β-catenin complex disassembly to cause β-catenin degradation. Moreover, curcumin directly inhibits GSK3β for quenching β-catenin release and nuclear translocation [28–30]. As a result of β-catenin inactivation, transcription factors: PPARγ and C/EBPα are also downregulated. β-catenin inactivation is also a target for attenuating cancers.

(*24*) *FOXO activation.* IP3k/AkT inhibition also leads to FOXO activation. Transcription factor: FOXO, a known tumor suppressor [45], is a positive downstream effector of PI3K/AkT [46]. AkT phosphorylates FOXOs, which blocks FOXO nuclear translocation and transcriptional activity. As the result of PI3K/AkT inhibition, FOXO dephosphorylation encourages its nuclear translocation and transcription activity resulting in FOXO upregulation with at least five-fold significance. (a) PI3K/AkT inhibition with FOXO3a upregulation decreases ROS production accompanied by ROS detoxification with elevated antioxidant enzyme (e.g., SOD2, catalase, GSH-Px) expression [47] for promoting antioxidant action. (b) Following the similar enhanced FOXO3a transcriptional activity antagonizes and destabilizes Myc oncogene [47], reflecting anti-cancers. (c) FOXO1 upregulation leads to enhanced apoptosis [45], while (d) FOXO1 activity is required for early phase in Treg differentiation, a component contributing to antiinflammation. (e) FOXO proteins also negatively regulate HIF [45], implying its antagonism against inflammation, angiogenesis, and possibly metastasis. Of particular interests, AMPK *per se* is proposed to be able to upregulate FOXO transcriptional activity independent of AkT modulation (please refer to above AMPK-dependent mechanism for insights).

(*25*) *Proapoptosis.* The enhanced apoptosis is proposed to be largely mediated by AkT inhibition alone and FOXO upregulation [45] resulting from PI3K/AkT inhibition along with SirT1 activation. Mechanistically, (a) Curcumin upregulates the extrinsic pathway [28–30,48] by (*i*) death receptor (e.g., DR4 and DR5) activation with binding to the pro-caspase ligand and (*ii*) inducing apoptosis with increased caspase-3/6/7/8. (b) In the intrinsic mitochondrial pathway, curcumin downregulates apoptotic inhibitors (e.g., BcL2 and BcL-xL) while promoting mitochondrial cytochrome C release through PUMA, NOXA, Bak, and BAX activations. As a consequence, Apaf1 activation in turn leads to caspase-3/7/9 activation for apoptosis.

(*26*) *NFκB inactivation.* NFκB inactivation by polyphenols is mainly mediated by PI3K/AkT inhibition, FOXO activation, and IKK inhibition. Curcumin, for instance, inhibits TLR4-induced IKKα/β phosphorylation; the resulting blocked release of IκB results in NFκB inactivation. Alternatively, curcumin inhibits AkT and its consequent IκB phosphorylation, similarly leading to NFκB inactivation and disfavoring cell proliferation [49–52].

(*27*) *ERK inhibition.* Curcumin inhibits MAP3K/MAP2K and in turn MAPK (JNK, p38, and ERK) activation, thereby downregulating AP-1-mediated transcription activity for TNFα, iNOS, and COX-2 expression [49–52], presenting anti-inflammatory in addition to anti-proliferative activities.

(*28*) *JAK/STAT inhibition.* Curcumin could inhibit JAK that otherwise phosphorylate STAT3, thereby blocking STAT3 dimerization and nuclear translocation. Such JAK/STAT attenuation exhibits anti-inflammatory (e.g., repressed proinflammatory genes) and anti-cancer (e.g., induced apoptotic proteins, suppressed apoptotic inhibitors and c-Myc oncogene) activities [49–52]. Similarly, resveratrol prevents JAK phosphorylation, thereby inhibiting STAT1 phosphorylation and transcriptional activity [53, 54]. In a study by Noh *et al*. [55] has revealed that such JAK/STAT1 inhibition by resveratrol extends to indoleamine 2,3-dioxygenase (IDO) suppression for cancer immunoprotection.

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(*29*) *IKK/JNK inhibition*. EGCG, an example, inhibits inflammatory serine/threonine kinase (e.g., JNK or IKK) directly or as a result of AkT inhibition to ensure antiinflammation (e.g., NFκB inactivation). In addition, such JNK/IKK inhibition attenuates insulin resistance; otherwise, JNK/IKK compete tyrosine phosphorylation on insulin receptor substrate (IRS).

(*30*) *ACE inhibition*. ACE inhibition by polyphenols presents two-fold significance in antiinflammation and antioxidation in view of ATII triggering ROS, cytokine, and chemokine production. Most flavonoids are reported to be competitive inhibitors of ACE [56]. Anthocyanins, flavonols (e.g., quercetin, kaempferol, and myricetin), and flavanol (e.g., catechins, epicatechins, and their polymers) are effective ACE inhibitors. Flavonoid precursor molecules chalcones (butein) and their pyrazole derivatives also dose-dependently inhibit ACE *in vitro*. Methylated epigallocatechin-3-*O*-(3-*O*-methyl) gallate is much effective inhibitory than its parent molecule epigallocatechin-3-*O*-gallate. ACE inhibitory properties of flavones remain unclear; however, isoflavones (e.g., genistein, daidzein, and glycetin) decrease ACE gene expression and enzyme activity.

(*31*) *α-glucosidase inhibition*. Polyphenols (flavones, flavonols, flavanones, isoflavones, catechins, and anthocyanidin) inhibiting α-glucosidase [57] reduces glucose inputs from dietary carbohydrates, certainly lowering hyperglycemic risk.

(*32*) *PDE4 inhibition*. Independent of inhibition on mitochondrial ATPase, resveratrol [20] inhibits cAMP-degrading PDEs (e.g., PDE4), resulting in accumulated cAMP that activates Epac1 for in turn stimulating PLCϵ. PLCϵ-mediated CamKII activation phosphorylates RYR2, further activating CamKKβ for AMPK activation.

(*33*) *Direct mTOR inhibition*. There is evidence for direct inhibitions on mTORC1 by phenolic phytochemicals. Resveratrol significantly increases the association between mTOR and its negative regulator (DEPTOR), thereby downregulating mTOR activity [58]. Curcumin decreases total expression of mTOR, Raptor, and Rictor protein and mRNA levels [59]. Without affecting upstream kinase activities and TSC1/2 interaction, curcumin is also able to dissociate raptor from mTORC1 [60].

(*34*) *Attenuated ET-1 production and signaling*. Nuclear exclusion of phosphorylated FOXO1 by EGCG results in downregulation of ET-1 promoter, thereby suppressing ET-1 expression and its activity [61]. Similarly, hydroxysafflor yellow A (HSYA), resveratrol, and quercetin reduce ET-1 production. In addition, green tea or EGCG downregulates ETA receptor, blocking ET-1 signaling for anti-hypertension and hypertrophy.

(*35*) *Anticoagulation*. Significantly prolonged TT, aPTT, and PT have been reported *in vitro*, *in vivo*, or *ex vivo* in response to polyphenols. (a) thrombin inhibition [62,63]. Curcumin and its derivative bisdemethoxycurcumin, cyanidin, quercetin, silybin, cyanin, (+)-catechin and (-)-epicatechin inhibit thrombin amidolytic activity; in addition, cyanidin, quercetin, and silybin suppress thrombin proteolytic activity. Aglycones act as competitive thrombin inhibitors, while chokeberry extract significantly inhibits thrombin amidolytic activity. (b) FXa inhibition [63–65]. Flavonoids: procyanidin B2, cyanidin, quercetin, and silybin bind S1–S4 pockets in vicinity of the FXa active site and block access of substrates to Ser195, thereby directly inhibiting FXa amidolytic activity. Curcumin and its derivative bisdemethoxycurcumin also inhibit FXa activity. (c) protection from FVII activation [66]. Tannic acid, delphinidin, hamamelitannin, (-)-epicatechin gallate, and 3,5-di-O-caffeoylquinic acid bind plasma hyaluronan-binding protein and inhibit FVII autoactivation (autoproteolysis). (d) TF suppression/encryption [67]. Grape and its products with high content of polyphenols exert anticoagulation by suppression of TF synthesis in blood mononuclear cells and VECs. In a recent personal communication, antiinflammatory HSYA (a phenolic related flavonoid component from *Carthamus tinctorius* L.: 3,5,6-trihydroxy-2(*E*)-[1-oxo-3-(4-hydroxy phenyl)-2-propenyl]-4,6-bis[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxyl-methyl) oxan-2-yl]-2,4 cyclo-exadien-1-one) suppresses OxLDL-induced TF expression *in vitro/in vivo* models, which is mediated by PPARγ upregulation and attenuated p38 MAPK phosphorylation/activation. Rutin (flavonoid) has long been recognized as an anticoagulant for possible prevention of heart attack and stroke, which is mediated by its inhibition on protein disulfide isomerase that de-encrypts TF for initiating the extrinsic coagulation pathway and robusting thrombin formation. (e) other actions. Aronia melanocarpa or seeds of Vitis vinifera prolong clotting time and decrease the maximal velocity of fibrin polymerization and FXIIIa amidolytic activity in human plasma [68]. However, there is no evidence thus far whether polyphenols have any effects on natural anticoagulants (e.g., TFPI, APC, or AT III).

(*36*) *PKC inhibition*. Polyphenol superfamily generally inhibits PKC by several mechanisms: competition with binding of Ca2$^+$, ATP, the kinase catalytic domain, *etc*. as well as inhibition of PKC expression or translocation to membrane [69]. (a) PKC downstream signaling includes UDP-glucuronosyltransferase, MAPK/c-JUN, ERK, and EGFR, finally leading to upregulations on transcription factors: NFκB, AP-1, and early response gene-1. (b) PKC also involves in cell proliferation, which is mediated by MAPK activation and the above upregulated transcription factors. Thus, PKC inhibition exhibits antiinflammation, anti-proliferation, *etc*. as well as downregulated cell signaling.

(*37*) *MAPK inactivation*. Curcumin inhibits MAP3K/MAP2K and in turn MAPK (JNK, p38, and ERK) inactivation, thereby downregulating AP-1-mediated transcription activity for TNFα, iNOS, and

COX-2 expressions [28–31]. Thus, MAPK inactivation presents anti-inflammatory in addition to anti-proliferative activities.

(*38*) *Secretase inactivation.* Curcumin and other polyphenol [28–31,70] inactivates $\alpha/\beta/\gamma$ secretases that otherwise cleave amyloid precursor protein (APP) into amyloid β protein (Aβ). Aβ accumulation is a known characteristic of AD blocking neurotransmission along with intracellular neurofibrillary tangle formation.

(*39*) *Monoamine oxidase inhibition.* Resveratrol, curcumin, and quercetin directly inhibit monoamine oxidase that otherwise catabolizes neurotransmitters (e.g., 5-HT, epinephrine, DOPA, dopamine, *etc*.); therefore, polyphenols exhibit antidepressive property and cognitive improvement [31,32].

3.4 Other Actions

Polyphenols are also able to modulate protein expression and proceed immunoregulations, achieving up or down-regulation for disease prevention and antagonism. Epigenetic modulation and gut microbiota alteration by polyphenols have also been reported.

(*40*) *Downregulation on TLR expression.* To arrest inflammatory initiation and propagation, polyphenols such as curcumin, kaempferol-3-*O*-sophoroside, and EGCG inhibit TLR2/4 expression [71], which could reduce wide-range of inflammatory responses such as LPS, IL-1α/β, IL-6, TNFα, and HMGB1 release/signaling.

(*41*) K^+ *channels activation.* In an EC-independent fashion for vasodilation, resveratrol directly opens K^+ channels including KATP and BKCa expressed on VSMC where extracellular $Ca2^+$ influx and intracellular $Ca2^+$ release are also suppressed [72].

(*42*) *Upregulation on paraoxonase 1.* Quercetin increases paraoxonase 1 mRNA and protein expression, up-regulating paraoxonase 1 activity. Paraoxonase 1 is a HDL-associated enzyme displaying esterase and lactonase activity; paraoxonase 1 metabolizes toxic OxLDL or OxHDL, thus protecting LDL and HDL from oxidation [73], showing cardioprotection.

(*43*) *PAI downregulation.* By stimulating binding of upstream stimulatory factor-2 to two distinct E-box sequences, quercetin downregulates PAI-1 promoter, thus resulting in suppressed PAI-1 expression in human coronary artery ECs [74]. Polyphenols including curcumin, quercetin, resveratrol, and EGCG and its derivatives (octaacetate and theaflavin digallate) act as potential PAI-1 inhibitors to reduce PAI-1 production [75], favoring fibrinolysis and resolution of blood clots. Similarly, grape ingredients suppress PAI-1 levels [76,77].

(*44*) *tPA upregulation.* Quercetin induces tPA expression, which is mediated by functional Sp1-binding element in tPA promoter and p38 MAPK pathway [78]. Similarly, catechin, epicatechin, and resveratrol in red wine also induce tPA and u-PA *in vitro* [79].

(*45*) *Epigenetic modulations.* Epigenetic modulations, including regulations on DNA methylation, histone modification, and non-coding RNA (miRNA) effects, could offer cardioprotection and anti-cancer action, *etc*. EGCG inhibits DNA methyltransferase activity in various experimental and clinical studies [80–82]. Polyphenols also target histone deacetylase 6-related pathways. EGCG decreases the expression of oncogenic miRNAs (miR-92, miR-93, and miR-106b) and to increase the expression of tumor-suppressor miRNAs (miR-7-1, miR-34a, and miR-99a) in human cancer cells, while curcumin up-regulates miR-22 and down-regulates miR-199a, presenting improved cancer outcomes. Interestingly, polyphenolic antioxidation could in part contribute to epigenetic modulation, which remains to be elucidated.

(*46*) *Immunoregulation.* Polyphenols modulate immune responses in both the innate and adaptive systems, having either stimulatory or inhibitory effects including self-tolerance, anergy, *etc*. [83–86]. (a) Pterostilbene, a resveratrol analogous, suppresses DC activation and promoting Treg cell development and green tea polyphenol EGCG induces Treg cells. Dietary polyphenols (b) downregulate DC antigen presentation by CD83, CD80, CD11c, and MHC II and immune-modulate MΦs (e.g., antigen presentation, phagocytosis, cytokine production: M1/M2 polarization), (c) increase proliferation of B cells (antibody IgA/E/M/D production) and T cells (cytokine production, cytotoxic destruction, *etc*.), (d) suppress T differentiation into Th1, Th2, Th17, Th22, and Th9 cells, and (e) activate NKs (cytolytic perforin and granzyme B secretion). Accordingly, polyphenols confer immunomodulatory effects against allergic reaction and autoimmune disease largely by inhibition of autoimmune T cell proliferation, downregulation of proinflammatory cytokines (e.g., IL-6, IL-1, IFN-γ), enhanced Treg development, shifted Th1/2 balance, and decreased Th17 cells.

(*47*) *Altered gut microbiota.* As a prebiotics, polyphenols could alter the landscape of gut microbiota/microbiota diversity [87–89]. For instance, (a) resveratrol supplementation suppresses *Parabacteroides johnsonii*, *Alistipes putredinis,* and *B. vulgatus* induced by high-fat, which is proposed to enhance GLP-1 secretion [90]. (b) Pomegranate extract rich in gallic and ellagic acid enhances the total growth of *Bifidobacterium* spp. and *Lactobacillus* spp. without affecting *C. coccoides-E. rectale* and the *Clostridium histolyticum* groups [91]. (c) Green tea [92] increases the survival of *Bifidobacteria. Bifidobacterium* and *Lactobacillus* are known probiotics beneficial to food allergy. (d) Polyphenols decrease in *Bacteroides acidifaciens*, but increase in *Ruminococcus gnavus* and *Akkermansia mucinphilia*, [85] which in turn induces Tregs while suppressing inflammatory Th1/Th17 cells, confering anti-inflammation. (e) Curcumin is in favor of beneficial microbiota (*Bifidobacteria, Lactobacilli*) that are butyrate-producing bacteria, while it reduces the abundance of the

pathogenic ones (*Prevotellaceae*, *Coriobacterales*, *Enterobacteria*, *Bacteroidaceae*, and *Rikenellaceae*) that are often associated to the onset of systemic diseases such as AD, CRC, *etc*. It is also noted that microbiota (*Bifidobacteria longum*, *Bifidobacteria pseudocatenulaum*, *Enterococcus faecalis*, *Lactobacillus acidophilus*, and *Lactobacillus casei*) could be able to metabolize curcumin. The reciprocal relation between polyphenols and gut microbiota could be expected to promote human health.

4. Biological/Physiological Functions

Polyphenols with multiple targets (Fig. 2) readily offer broad antagonisms against disease development and progression including inflammation, CVD, diabetes, obesity, cancer, neurodegeneration, and infection; among which, oxidative stress and inflammation really play critical roles in pathogenic developments. Table 1, if not exclusively, summarizes polyphenolic actions in comparison with common approaches to combating pathological conditions.

4.1 Anti-Oxidative Stress

Oxidative stress defines overload ROS/RNS and pro-oxidants without appropriate/coordinated protection by antioxidants, possibly triggering pathologies. Biological system is constantly under oxidative stress, not only living in 20% oxygen (O_2) atmosphere, but also hypoxia (ischemia) stabilizing HIF1α to upregulate NADPH oxidase (NOX) (superoxide anion ($O_2\bullet^-$) formation) or to turn on downstream angiogenic gene (e.g., *VEGF*) expression. Oxidative stress serves as a molecular mechanism to mediate diverse disease progression and pathogenesis.

In a classical view of singlet O_2 metabolism, molecular O_2 is utilized by biological systems followed by a consequence of formations of $O_2\bullet^-$, hydrogen peroxide (H_2O_2), hydroxyl radical (OH$\bullet$), and H_2O in step-wise one-electron sequential reductions [93]. $O_2\bullet^-$, H_2O_2, and OH$\bullet$ are three major reactive oxygen species (ROS), all of which are cytotoxic and exhibit damaging effects on biological components including DNA damage, lipid/cholesterol oxidation, lipoprotein oxidation, protein oxidation, and membrane disruption [94].

ROS derives from either intrinsic or extrinsic sources. (a) Intrinsic ROS sources include that (*i*) ROS is by-products of mitochondrial respiration, especially in mitochondrial dysfunctions in complex I/II/III or IV; (*ii*) during infection triggering innate immunity, $O_2\bullet^-$ is the main product from NOX (also known as respiratory burst oxidase mainly in neutrophils) to kill invading pathogens. NOX catalyzes the one-electron reduction of O_2 to generate $O_2\bullet^-$ in the presence of NADPH in microsomal electron transfer chain. In other signaling systems, TNF stimulates the formation of mitochondrial $O_2\bullet^-$, while vascular smooth muscle cells (VSMC) produces $O_2\bullet^-$ in response to AT II; (*iii*) endogenous H_2O_2 could derive from respiratory burst through NOX2 following infection; $O_2\bullet^-$ is then converted

to H_2O_2 by superoxide dismutase (SOD). Mitochondrial H_2O_2 production can also be activated by defective respiratory functions or blocking complex I (by retenone) or complex III (by antimycin A); (*iv*) endogenous H_2O_2 forms OH$\bullet$ and OH$^-$ anion through the non-enzymatic Fenton reaction when $Fe2^+$ is oxidized to $Fe3^+$ or during other transition metal oxidations. H_2O_2 can also be decomposed by catalase, GSH-Px, or peroxiredoxin to H_2O; (*v*) xanthine oxidase is proposed to contribute to ROS production; (*vi*) other intrinsic sources could also consist of advanced glycation end-product (AGE), ATII, and pheomelanin. (b) Extrinsic ROS sources include smoking (e.g., some 10^{14} free radicals per inhalation), alcohol (e.g., CYP2E1 induction for $O_2\bullet^-$ and H_2O_2 generation and reduced cellular GSH while inducing iron accumulation and TNF-α production), xenobiotic oxidation (cytochrome p450 reducing molecular oxygen in the proceeding of xenobiotic oxidation through electron transfer from NAD(P)H. $O_2\bullet^-$, H_2O_2, and OH$\bullet$ are generated as intermediates when heme center undergoing oxidation with conversion of $Fe2^+$ to $Fe3^+$ for radical formation), hypoxia/reperfusion (e.g., microsomal NOX induction for $O_2\bullet^-$ production), or infections (e.g., NOX activation), all of which participate in a series of enzymatic reactions in response to diverse environmental insults (extrinsic oxidative stress), initiating biological oxidations and elevating endogenous ROS. (c) Similarly, reactive nitrogen species (RNS) including reactive nitrogen intermediates (RNI) exhibit diverse biological damages often in crosstalk with ROS. RNS includes peroxynitrile (ONOO$^-$), nitroxyl (NO$^-$), nitrosyl chloride (NOCl), and nitrogen dioxide (NO$_2$), all of which are toxic to biological functions. For instance, $O_2\bullet^-$ effectively reacts with NO; the resulting OONO$^-$ undergoes notorious diverse radical reactions including oxidations and nitrosations, which is even more biological toxic and damaging (e.g., induced apoptosis, cell death). (d) In addition, damaging radicals (electrophilic) undergoing non-enzymatic reactions in a fashion of chain-reaction with biomolecules (e.g., DNA, lipids, cholesterol, lipoproteins, proteins, and biomembranes) thus propagate radical formations and intensify oxidative stress.

Natural oxidative defense includes antioxidants (e.g., vitamin C/E, GSH, α-lipolic acid, N-acetylcysteine, ubiquinol/CoQ, NO, Se, and many antioxidants (either $1°$ or chain breakers for radical chain reactions of propagation)) and antioxidant enzymes (e.g., catalase, SOD, GSH reductase, GSH-S-transferases, GSH-Px, quinone reductase, HO, paraoxonase, *etc*.), removing free radicals (scavenging or breaking).

The classical antioxidant actions of polyphenols are able to scavenge radical, chelate metal, upregulate endogenous antioxidant enzymes for biological detoxification, and inhibit ROS production from mitochondrial respiration, respiratory burst, and xanthine oxidase (please refer to 3.1 (*1*) to (*6*)). The protection from DNA damage, membrane disruption, and lipid/cholesterol, lipoprotein, and carbohy-

Table 1. Major polyphenolic actions are comparable to common therapeutic approaches to inflammation, CVD, diabetes, obesity, cancer, neurodegeneration, and viral infection.

Antagonism	Major Polyphenolic Action	Common Therapeutic Approach
Antiinflammation	AMPK activation; NFκB inactivation; IP3K inhibition; downregulated TLR expression; NLPR3 inactivation; upregulated autophagy; JAK/STAT inhibition; IKK/JNK inhibition; downregulated Th1/Th2 ratio; anticoagulation; anti-platelet; PDE inhibition; *etc.*	glucocorticoids; aspirin; statins; IVIG; adenosine analogs; anti-cytokine mAb; cytokine receptor inhibition; cytokine signaling inhibition; complement inhibition; HDAC inhibitors; PDE4 inhibitors, *etc.*
Anti-CVD	AMPK activation; hypolipidemic actions; HMG-CoAR inhibition, LPL upregulation; ANGPL4 repression; SREBP1-c suppression; anticoagulation; eNOS activation; PDE inhibition; ACE inhibition; COX1 inhibition; downregulated P-selectin; PPARα agonism; K$^+$ channel activation; paraoxonase 1 upregulation; PAI downregulation; tPA upregulation; *etc.*	statins; aspirin; α/β-blockers; ACE inhibitors; PDE inhibitors; AT receptor blockers; tPA; anticoagulants (warfarin, anti-FXa, thrombin inhibitor, *etc.*); anti-IL1β; ACAT inhibitor; sGC inhibitor; *etc.*
Anti-diabetes	AMPK activation; eNOS activation; insulin sensitivity; α-glucosidase inhibition; suppressed β cell apoptosis; increased GLP-1 release; *etc.*	metformin; sulfonylurea; GLP-1 receptor agonists, GLP-1 ligands; DDP-4 inhibitors; Na$^+$/glucose pump inhibitors; insulin replacement; *etc.*
Anti-obesity	AMPK activation; lipogenic/adipogenic inhibition; suppressed food intake; antiinflammation; *etc.*	pancreatic lipase inhibitors; serotogenic drugs; CCK mimetics; thermogenic drugs; amylin mimetics; leptin analogues; ghrelin antagonists; GLP-1/GLP-1R analog/ agonist; MC4R agonist; NPY antagonists; bariatric surgery; *etc.*
Anti-cancer	antioxidation; AMPK activation; antiproliferation; proapoptosis; autophagy upregulation; PI3K/ AkT/ mTOR inhibition; JAK/STAT inhibition (IDO suppression); suppressed oncogenic factors (cMyC, HIF-1α, AP-1, STAT3, Wnt/β-catenin, NFκB, androgen and estrogen receptors); PKC inhibition; upregulated suppressive transcription factors (FOXOM1, NRF2,); gene stability; suppressed metastasis (e.g., EMT); suppressed angiogenesis; suppressed EGFR expression; p53 activation; inhibitor of estrogen/androgen biosynthesis; immuno- modulation/ regulation; T activation; *etc.*	**chemoprevention**: COX inhibitors; bexarotene; metformin; retinoid ATRT; aromatase inhibitor; bisphosphonates; zoledronic acid; *etc.* **chemo/target -therapy**: signaling kinase inhibitors; NFκB inhibitor; anti-EGFR/ VEGFR/HER2 mAbs/inhibitors; BcL-2/ XIAP inhibitors; XPO1 inhibitor; IDO inhibition; 5-FU; platinum; PARP inhibitors; taxol; *etc.* **immunotherapy**: checkpoint blockade, ATC; CAR-T; *etc.* **radiation & surgical procedures**
Anti-degeneration	BDNF activation; mTOR inhibition; downregulated Aβ; antiinflammation; γ-secretase inhibition; monoamine oxidase inhibition; *etc.*	rapamycin; anti-Aβ mAb; Ach; Ach esterase inhibitor; L-dopa; monoamine reuptake inhibitor; 5-HT; γ-secretase inhibitors; trem-2 Aβ; *etc.*
Anti-viral infection	inhibited viral entry; reverse transcription inhibition; autophagy upregulation, *etc.*	neutralizing Aβ; protease inhibitors; reverse transcriptase inhibitors; vaccines; *etc.*

drate/protein oxidations could exhibit anti-cancer, anti-diabetes, anti-obesity, anti-neurodegeneration, *etc*. Moreover, it is well-established that ROS significantly contributes to the initiation of inflammation (refer to as oxidation-inflammation axis) [95–100]; therefore, polyphenols certainly complement their anti-inflammatory efforts by disrupting the ROS-inflammation axis. Concerning cardioprotection, for instance, the anti-oxidative stress is mainly achieved by the classical antioxidation, which is also ensured by ACE inhibition interrupting ROS generation in response to AT-II and by the anti-inflammatory actions blocking the axis in view of ATII being an endogenous source of ROS.

4.2 Antiinflammation

Historically, inflammation presents as heat, redness, swelling, and pain, which is now understood in response to elevated cytokines and chemokines with major responsibilities for driving diverse non-communicable diseases including diabetes, obesity, CVD, neurodegeneration, non-alcoholic fatty liver disease (NAFLD), cancers, chronic kidney disease, inflammatory bowel diseases (IBD: Crohn's, colitis), irritable bowel symptoms (IBS), *etc*.

4.2.1 Onset of Inflammation

(a) Upon infection (bacterial, viral, parasitic, *etc*.) recognized by pattern recognition receptors (PRR; e.g., TLRs, RIRs, *etc*.), it often triggers inflammation with elevated cytokine and/or chemokine release by innate immune cells such as MΦs and neutrophils; in this regard, inflammation is part of innate immune for activating and proceeding adaptive immunity. Without proper control, inflammation, however, often leads to pathological consequence. For instance, cytokine storm without proper antiinflammation and resolution of inflammation damages tissues developing pathological manifestations. (b) Non-infectious conditions such as trauma, surgery, environmental insults, *etc*. also often trigger inflammatory responses. For instance, tissue injuries (e.g., ischemic heart attack or myocardial infarction) and the one triggered by microbes, often cause necrotic/apoptotic cell death and matrix damages, which releases host danger products such as high mobility group protein 1 (HMGB1), IL-1/33, mtDNA, or mitochondrial N-formyl-peptide (f-Met-Leu-Phe; fMLP) for triggering local inflammation through DAMP receptors [101]. Upon injury or infection, HMGB1 is released passively from necrotic cells or by active secretion from MΦs and monocytes via IFNβ-mediated JAK/STAT pathway, which is readily responsible for triggering inflammatory responses in lethal endotoxemia and sepsis. (c) Autoimmunity has long been proposed to lead to chronic inflammation. Autoantibodies activate complements, which could contribute to acute/chronic inflammation. The elevated autoantibodies, for instance, anti-CRP in systemic lupus erythematosus, often target opsonins to form ternary pyrogenic im-

mune complex with apoptotic materials, which shifts from classical opsonin functions in facilitating phagocytosis of apoptotic/necrotic cells toward promoting release of proinflammatory cytokines (e.g., IL-8, TNF) by MΦs [102]. In an experimental model, anti-CD3/CD28 (HIT3A/CD28.2) could result in IκBα degradation, an inflammatory prerequisite. (d) Furthermore, blood coagulation-inflammation axis [103–106] and oxidative stress-induced inflammation [107] make inflammation occurring for diverse pathological manifestations. For instance, coagulants (FVIIa, FXa, FXIIa, KK, thrombin, *etc*.) trigger inflammatory cytokine elevation. Oxidation (ROS) readily contributes to the initiation of inflammation [95–100]; namely, ROS is essential for NLRP3 activation.

Inflammation occurs when pro- and anti- inflammation systems are out of balance plus defects in resolution of inflammation [108]. (a) Overwhelming proinflammation includes signaling activations (upregulated NFκB, HIF, mTORC1, PI3K/AkT, Ras/Raf/MEK/ERK, and JAK/STAT), complement activation, autophagy inactivation, and ER stress as well as elevated inflammatory mediators (e.g., cytokines, chemokines, TNF, leptin, extracellular ATP, clotting factors, BK, arachidonate (AA) metabolites, ATII, AGE, PAF, CRP, plasmin, ROS, calpains, CD40/CD40L, growth factors, histamine, other endogenous DAMP (HMGB1, mtDNA, TSLP), *etc*. Interestingly, several extracellular matrix components such as MMP2, TNF converting enzyme, and proteoglycan play activating roles in inflammation, while protease Omi suppresses inflammation. (b) Anti-inflammatory events mainly involve AMPK activation, FOXO activation, SirT1 activation, autophagy activation, NFκB inactivation, mTORC1 inhibition, M2 polarization, PI3K/AkT inhibition, JAK/STAT inhibition, complement inhibition, anticoagulation, PAR inhibition, PPAR agonism, HDAC inhibition, PDE4 inhibition, cytokine/mediator antagonisms (e.g., anti-TNF, receptor antagonists, anti-cytokine, LPS antagonism), *etc*. (c) Resolution of inflammation is largely achieved by endogenous anti-inflammatory lipid mediators (lipoxin A4 (LXA4) derived from AA, 15-epi-LXA4 derived from AA, Rvs derived from EPA or DHA, RvD1/2/3/4 derived from DHA, protectin and maresin derived from DHA). Other pro-resolving lipid mediators are also of resolution and antiinflammation: (*i*) endogenous electrophilic nitrated fatty acids [109] (naturally occurring E-9/E-10 NO_2-oleic acid and E-10/E-12 NO_2-linoleic acid) suppressing IKK phosphorylation, NFκB nuclear translocation, TRAF6 recruitment (TLR4 signaling), STAT-1 phosphorylation and nuclear translocation, neutrophil/platelet activation, AT1 receptor, BcL-xL, xanthine oxidoreductase ($O_2 \bullet^-$ production), NOX ($p47^{phox}$ and $gp91^{phox}$), 5-LOX, and the expression of TLR4, cytokine (TNF-α and IL-1β), VCAM-1/ICAM-1, MMP, and iNOS. The abilities to activate Nrf2/keap1, PPARγ, AMPK, ERK1/2, CaMKKβ, caspase-8/9, Bad, MAPK phosphatase-1, eNOS phospho-

rylation at Ser1179, and the expression of eNOS, HO-1, and heat shock factors are consistent with the antiinflammatory potentials. Independent of cGMP-mediated NO actions, nitrated fatty acids undergoing nitroalkylation modify protein functions and enzyme activities, which is similar to direct protein S-nitrosylation consequences in mediating antiinflammation. Nitrated fatty acids are also proposed to release NO; (*ii*) lysophospholipid inactivates ERK/p38, thereby showing antiinflammation by the consequent suppression of NFκB activation and TNFα expression. Sphingosine-1-phosphate promotes NO release, presenting its anti-inflammatory action; (*iii*) PGI2 blocks NFκB translocation/activation, while PGJ2 confers antiinflammatory effect via inactivating NFκB by forming an adduct with NFκB; (*iv*) conjugated linoleic acid, a PPARα agonist, decreases TNFα and IL-6 production, which is accompanied by FOXp3+ Treg expansion, increases in ex vivo lymphocyte proliferation, and IL-2 or IFNγ production in stimulated T cells; (*v*) short chain fatty acids, main metabolic products of anaerobic bacteria fermentation in the intestine, inhibit HDAC and act on leukocytes and endothelial cells through GPR41 and GPR43 receptors to reduce production of cytokines (TNFα, IL-2, IL-6, and IL-10), NO, and chemokines (e.g., MCP-1 and CXCLs). Its suppression of HMGB1 release thereby attenuates septic risk; (*vi*) n-3 FA, n-6 AA, and PGD2-derived cyclopentenone-containing lipid peroxidation products offer anti-inflammatory actions [110]; and (*vii*) possible antiinflammatory and pro-resolving roles of PGF2α remain largely unclear and elusive. PGF2α could reverse exacerbation of inflammation by functioning as an endogenous agonist (selective FP receptor agonist fluprostenol) during the resolution phase after inhibition of COX-2 with a highly selective COX-2 inhibitor.

4.2.2 Common Anti-Inflammatory Therapeutic Strategies

(a) Endogenous and exogenous glucocorticoids are common anti-inflammatory agents, reducing cytokine-induced genes or mediators [111]. (*i*) Glucocorticoids inhibit the production of TSLP, cytokines, chemokines, adhesion molecules, and other inflammatory mediators. They suppress NFκB-dependent transcription by upregulating MAPK phosphatase-1 to dephosphorylate p38 MAPK; otherwise, p38 MAPK transactivating NFκB via p65 serine phosphorylation in turn leading to NFκB-dependent transcription is essential for proinflammatory cytokine gene expression. (*ii*) As a result of downregulated NFκB, glucocorticoids also suppress COX-2, iNOS, and ICAM-1 expression. (*iii*) From immunology viewpoints, glucocorticoids suppress T effectors; T effector proliferation requires IL-2, IL-4, IL-5, IL-17, and IFNγ. (*iv*) Glucocorticoids activate MΦ phagocytosis of apoptotic cells while increasing the expression of IL-1 decoy receptor and promoting MΦ to release anti-inflammatory IL-10 and TGFβ. (*v*) Corticosteroids induce MAPK phosphatase

1, inhibit JNK, inactivate NFκB and AP-1, block PLA2, COX-2, and lipocortin-1, and reduce PG and LT biosyntheses. As the result of suppressed production of IL-1, TNF-α, GM-CSF, IL-3, IL-4, IL-5, and CXCL 8, corticosteroids readily exhibit antiinflammation. (b) Antiinflammatory IVIG contains diverse soluble proteins that could neutralize cytokines and chemokines and antagonize their corresponding receptors. Clinically, (*i*) IVIG readily improves glucocorticoid response/sensitivity possibly mediated by its improved receptor binding or suppressed proinflammatory cytokine production. (*ii*) Mediated by Fab, IVIG suppresses or neutralizes autoantibodies and cytokines, neutralizes activated complement components, restores idiotypic-antiidiotypic networks, blocks leukocyte-adhesion-molecule binding, targets specific immune cell-surface receptors, and modulates DC maturation and function. (*iii*) Through Fc domain, IVIG confers anti-inflammatory actions by blockade of the FcRn and FcγR activation, upregulation of inhibitory FcγRIIB, and immunomodulation by anti-inflammatory sialylated IgG segments. (*iv*) IVIG also lowers systemic HMGB1 release [112]. (c) Extracellular adenosine dampens inflammation, which is mediated by four distinct adenosine receptors: A1, A2A, A2B, and A3. Concerning clinical anti-inflammatory functions, A1 receptor activation during intravenous administration of adenosine for the treatment of supraventricular tachycardia. A2A activation on inflammatory cells such as neutrophils or lymphocytes attenuates inflammation. A2B activation in response to tissue hypoxic adaptation suppresses ischemia and reperfusion. A3 adenosine receptor activation may relief inflammatory dry eye syndrome. (d) Statins are recognized antiinflammatory based upon AMPK activation [113], IKK inhibition, IKK-independent NFκB inactivation, JAK/STAT inhibition [114,115], PI3K/AkT/mTOR inhibition, FOXO upregulation, eNOS activation, Nrf2 activation, HO-1 activation, increased IL-10, attenuated proinflammatory biomarkers (e.g., CRP, IL-6, and TNF) [115,116], suppressed CD40 expression [117], decreased MHC II expression, depressed tissue factor expression and its initiated blood coagulation, and Treg accumulation [118]. Statins also promote efferocytosis and cysteine S-nitrosylation of COX-2 for Rvs (e.g., 15-epi-LXA4) production [119], both of which are considerably anti-inflammatory. The ability to promote S-nitrosylation of thioredoxin at Cys69 subsequently stimulates the antioxidative activity to facilitate ROS scavenging. In the context of its classical effects on cholesterol lowering, statins eventually prevent inflammasome (NLRP3) activation from cholesterol accumulation. Statins attenuate T cell activation by depleting membrane cholesterol and disrupting the integrity of lipid rafts that are essential to TCR and costimulatory molecule assemblies [120]. On the contrary, there is evidence for PI3K/AkT/mTOR and AkT/β-catenin activation by statins [121,122]; further research is needed to verify such discrep-

ancies in relation to anti-inflammatory mechanism(s). (e) Aspirin, a member of phytochemical family, is currently recommended for cancer prevention, cardioprotection, and antiinflammation in addition to its classical roles in COX inhibition and minor pain/fever relief. Apart from COX inhibition for attenuating inflammatory PGs and LTs species, aspirin effects include AMPK activation, suppressed TNF secretion, and the serine acetylation of COX-2 for the formation of antiinflammatory Rvs (e.g., 15-epi-LXA4) [123]. Other COX inhibitors (e.g., NS-398, celecoxib, *etc*.) block PGE2 production; recent studies have revealed that COX inhibitors could relieve influenza infection [124]. (f) Low NO concentration ($<$400 nM or under hypoxia) essentially facilitates HIF degradation and impairs HIF1α signaling. NO antagonizes EC adhesion and inhibits caspase (suppressed IL-1β/18 expression) while enhancing T cell expansion. The abilities of low level of NO to reduce BcL-2 family member expression and increase cytochrome C release certainly contribute to proapoptosis, thereby representing resolution of inflammation. Apoptotic immune cells are phagocytosized by MΦs, reducing the production of inflammatory mediators. Mechanistically, post-translational modification (S-nitrosylation) not only mediates NO actions, but also serves as anti-inflammatory mechanisms [125–127]. (*i*) S-nitrosylation of NFκB p65 (Cys38)/p50 (Cys62) results in suppressed NFκB binding to iNOS promoter, thereby attenuating iNOS expression. (*ii*) S-nitrosylation of AP-1 c-Jun and c-Fos DNA binding domains blocks AP-1 binding to DNA promoters of various proinflammatory target genes. (*iii*) S-nitrosylated IKK at Cys179 inhibits IKK activity and suppresses NFκB nuclear translocation, thus diminishing cytokine and COX expression. (*iv*) S-nitrosylation of MyD88 at Cys216 blocks its recruitment to TLR for proceeding TLR signaling. (*v*) S-nitrosylation has negative effects on EGF receptor (Cys166 and Cys305) and AkT (Cys224), thereby attenuating growth factor-mediated inflammation. (*vi*) S-nitrosylation suppresses CD40L-induced CD40 activation, leading to attenuated IL-1β, IL-12, and TNFα production. (*vii*) S-nitrosylation enhances SOCS1 expression. Clinically, endogenous or exogenous S-nitrosylating agents (e.g., ethyl nitrite, S-nitroglutathione, *etc*.) and NO donors (e.g., atorvastatin) are used for treating inflammation such as Crohn's disease, bronchopulmonary dysplasia, acute lung injury/acute respiratory distress syndrome, asthma, COPD, *etc*. (g) By blocking the ability of TRAF6 to phosphorylate IKK, miR-146b and miR-155 serve as negative feedback regulators in TLR-mediated signaling following the canonical LPS/MyD88/IRAKs/TRAF6 pathway. miR-125b directly inhibits TNF-α expression and NFκB transcription, while miR-let7 and miR-21 target TLR4 mRNA at the post-transcriptional level preceding MyD88 signaling. miR-21 also shows positive regulation on IL-10 production [128]. (h) Complement inhibition attenuates tissue injury/destruction, septic shock, mul-

tiple organ failure, hyperacute graft rejection, and various disorders [129]. (*i*) Endogenous soluble C-1 inhibitor is an anti-inflammatory reagent with therapeutic potential. (*ii*) Eculizumab and soliris (monoclonal antibodies against complement C5) suppress complement activation. (*iii*) Other antagonisms include C1-recombinant soluble complement receptor, antibodies to C3/C5 blocking the cascade reaction, neutralization of the complement-derived anaphylatoxin C3aR/C5aR/CD88, CD18/11b interference with C3R, and regulatory membrane-bound complement receptors (e.g., CR1/CD35, complement receptor-related gene y (crry; CR2/CD21), membrane cofactor protein (MCP/CD46), DAF/CD55, and CD59-protective receptors) [129]. (i) Heat shock response attenuates proinflammatory mechanisms and iNOS activity; it essentially stabilizes IκBα by depleting IKK-α and phosphorylated IKK-α. Such inhibition on NFκB-dependent transcription makes HSP anti-inflammatory [130]. Accordingly, heat shock blocks AT II-induced expression of IL-6 and ICAM-1. Immunologically, Treg induction and maintenance promoted by stress-induced HSP certainly contributes to antiinflammation. Specifically, (*i*) HSP90 activates eNOS [131] with concomitant reduction in $O_2^{\bullet-}$. (*ii*) In addition to reduced oxidative damages, HSP70 downregulates CD86 and MHC II expression while inhibiting TNF-α production [131]. HSP70 can also inhibit IFN-γ production by monocytes. HSP70 through TLR2 activates MyD88 and subsequent ERK phosphorylation that triggers IL-10 production [131]. HSP70 also exerts its anti-apoptotic function downstream of caspase-3-like proteases. (*iii*) HSP60 facilitates the maturation of pro-caspase-3 to its active form, while HSP32 functions as HO-1, an antioxidant enzyme.

HSP inducers include ischemia-reperfusion, physical exercise, heavy metals, toxins, radiation, UV-light, laser, decreased ATP levels, and pH/osmolarity changes. The pharmacological HSP inducers include bimoclomol, geranylgeranylacetone, α-lipoic acid, ansamycins, butyrate, prostaglandins, celastrol, terrecyclin-A, BRX-220, PLA2, and NO. TGFβ could induce HSP70 and HSP90 expression, which in part confers the antiinflammation of TGFβ [132]. It is also noted that AT II induces HSP27 and HSP70 expression and their phosphorylation; phosphorylated HSP27 and HSP70 in turn protect against AT II-induced inflammation [132,133]. (j) In the context of coagulation-triggered inflammation [103–106], anticoagulation could arrest inflammatory signaling. (*i*) Anticoagulants (e.g., inactivated FVIIa, direct FXa inhibitors, direct thrombin inhibitors, LMWH, heparins, and natural anticoagulants (TFPI, activated protein C (APC), and AT III) all suppress the extrinsic coagulation pathway and the generation of proinflammatory coagulant mediators (e.g., FVIIa, FXa, and thrombin). APC directly inhibits FVa, FVIIIa, and PAI; it broadly targets blood coagulation system including the extrinsic and intrinsic pathways as well as fibrinolysis, which makes it the most efficient anti-sepsis. Decreased IL-6 production

and inhibited iNOS account for APC anti-inflammatory nature. Recombinant human APC (drotrecogin alfa; DrotAA) is recommended in severe sepsis and DIC, resulting in dose-dependent reduced D-dimer and IL-6 without an increase in serious bleeding. APC inhibits HMGB1 release and its receptor (TLR2/4 and RAGE) expression [112]. ATIII also attenuates HMGB1 accumulation. Interestingly, anticoagulant protein soluble thrombomodulin functions as an antibody binding HMGB1, thereby reducing HMGB1 transmission. (*ii*) Concerning the intrinsic pathway, PA (urokinase) readily downregulates contact system with the consequence of lowering BK production and complement inactivation, preventing inflammation. C-1 inhibitor downregulates contact coagulation by inactivating KK and FXIIa, showing antiinflammation. Eecallantide (DX88) is a potent and specific inhibitor of plasma KK; DX88 reverses the increased vascular permeability. Aprotinin inhibits KK and suppresses BK release. ATIII-bound heparin and heparin sulfate inhibit FXII activation. Ecotin is a potent inhibitor for FXIIa and KK. Warfarin inhibiting vitamin K-dependent protease activations generally exhibits anti-inflammatory action [106]. (*iii*) PAR antagonism blocks the signal transmission of coagulant mediators that activates cells for eliciting proinflammatory cytokines, adhesion molecules, and growth factors. For instance, PAR-1 antagonist (SCH 79797) offsets plasmin-induced IL-8 expression and PGE2 release [134]. Refluden® suppresses MΦ adhesion [135]. A thrombin receptor antagonist (E5510) diminishes VEGF [136] or PDGF [136] expression. SCH79797 by blocking ERK activation also inhibits lung inflammation and influenza A virus replication [137], while PAR-2 antagonism via IFN-γ-dependent pathway prevents influenza infection [138]. PAR-2 peptide antagonists (FSLLRY-NH$_2$ and LSIGRL-NH$_2$) suppress *Serratia marcescens serralysin*-induced IL-6/8 expression [139]. Anti-PAR-2 antibodies and tryptase inhibitors (GW-45 and GW-61) cause significant decreases in IL-6 and IL-8 release from human peripheral blood eosinophils [140]. ENMD-1068 suppresses cytokine production, benefiting to inflammatory arthritis [141]. FUT-175 (6-amidino-2-naphthyl 4-guanidino-benzoate) consistent with PAR-deficiency eases IBD/IBS [142]. PAR-4 antagonist (P4pal-10) dose-dependently diminishes the severity of endotoxemia, systemic inflammation, and DIC [143]. (k) PPARs are antiinflammatroy [144]. Clinically, PPARs present protections from CNS, EC dysfunction, liver (e.g., NAFLD), and white adipose tissue inflammation, endotoxemia, LPS-induced cardiac and pulmonary inflammation, IBD (e.g., Crohn's disease), *etc*. (*i*) PPARα increases IκB expression and downregualtes NFκB, AP-1, and NFAT. PPARα favors switching to MΦ M2 polarization. PPARα agonist (Wy) decreases mRNA of *tnfa*, *mcp-1*, *mac-1*, *etc*. For instance, conjugate linoleic acid shows antiinflammation via PPARα agonism. (*ii*) PPARβγ prevents LPS-induced NFκB activation by downregulating ERK1/2.

PPARβγ prevents M2 switching back to MΦ M1 polarization. M1 MΦs display enhanced microbicidal capacity and secrete high levels of proinflammatory cytokines (TNFα, IL-1β, and, IL-6) and increased $O_2 \bullet^-$ and ROS/RNS radicals to increase their killing activity. In contrast, M2 MΦs are pro-resolving and anti-inflammatory by dampening proinflammatory cytokine levels, secreting ECM components, and promoting efferocytosis. (*iii*) PPARγ decreases not only cytokine expression, but also PMN infiltration. For instance, 15-deoxy-Δ-(12,14)-PGJ2, a specific ligand of the nuclear receptor PPARγ, reduces multiple organ failure and inhibits the expression of proinflammatory genes. Pharmacological PPARγ ligand (rosiglitazone) readily reduces the expression of iNOS, COX-2, ICAM-1, and P-selectin; thiazolidinediones (PPAR-γ agonists; e.g., rosiglitazone) reduces inflammation by activating glucocorticoid nuclear translocation and/or downregulating NFκB-mediated pathways. (l) Histone deacetylase (HDAC) inhibitors (e.g., valproic acid, sodium butyrate, and suberylanilide hydroxamic acid) suppress cytokine production, exhibiting immunosuppression and antiinflammation. HDAC inhibitors ensure acetylation of proiflammatory transcription factors (e.g., NFκB, AP-1, or NFAT-1) and their nuclear exclusion. It is also proposed that HDAC inhibitor is involved in caspase-1 suppression for blocking IL-1β release. (m) By increasing cAMP levels, PDE4 inhibitors (e.g., rolipram, piclamilast, roflumilast, analog cilomilast, phthalazinones, *etc*.) present a broad spectrum of anti-inflammatory effects. (*i*) Notably, the inhibitors attenuate LPS-induced TNF release from monocytes and MΦs. (*ii*) The inhibitors prevent NFκB from binding to DNA promoter and thus decrease VEGF expression and cytokine production. Clinically, they are used for treatment of inflammatory asthma, COPD, psoriasis, IBD, RA, *etc*. (n) Anti-IL-6 mAb (sarilumab) or decoy could relief SARS-CoV2 symptom (cytokine storm).

4.2.3 Polyphenolic Actions

(a) The effective polyphenolic anti-oxidative stress (please refer to 3.1 (*1*) to (*6*) & 4.1) readily suppresses ROS-inflammation axis, achieving antiinflammation. (b) Polyphenols target multiple inflammatory components [145] by antioxidant potentials (please refer to 3.1 (*1*) to (*6*)), AMPK activation (please refer to 3.2 (*7*)), inhibitions on PI3K/AkT, mTORC1, IKK/JNK, and JAK/STAT (please refer to 3.3 (*22*), (*33*), (*29*), and (*28*), respectively), suppressed HMGB1 release (please refer to 3.4 (*40*)), and TLR suppression (please refer to 3.4 (*40*)). As a result, polyphenols readily lead to NFκB, AP-1, HIF, and STAT inactivation (please refer to 3.2 (*11*), 3.2 (*18*), 3.3 (*26*)) with reduced proinflammatory mediators (e.g., PGE2, cytokines, adhesion molecules, growth factors, *etc*.). (c) Polyphenols sustain resolution of inflammation by SirT1 activation (please refer to 3.2 (*8*)), eNOS activation (please refer to 3.2 (*11*)), FOXO upregulation (please refer to 3.2

(*9*), 3.3 (*24*)), PDE inhibition (please refer to 3.3 (*32*)), and adiponectin elevation (please refer to 3.2 (*21*)). (d) In addition, polyphenol-induced anticoagulation (e.g., TF suppression, inhibited FVIIa/Xa amidolytic activities) and anti-platelet aggregation (e.g., COX inhibition; reduced TxA2) could arrest the coagulation-thrombosis-inflammation circuit [103–106]. (e) Polyphenols are also able to decrease Th1/Th2 for pro/anti-inflammatory cytokine secretion ratios *in vitro*, implying anti-immunoinflammatory potentials [86,145]. (f) Decrease in *Bacteroides acidifaciens*, but increase in *Ruminococcus gnavus* and *Akkermansia mucinphilia* [85] in turn induces Tregs while suppressing inflammatory Th1/Th17 cells, also showing antiinflammation by polyphenols.

Such a wide range targeting the initiation (please refer to 4.2.1) and pathophysiology (please refer to 4.2.1) of inflammation by polyphenols (Fig. 2) is analogous to common pharmacological approaches (please refer to 4.2.2 and Table 1) including glucocorticoids (suppressing NFκB for COX-2, iNOS, and ICAM-1 expression, and T effectors for IL-2, IL-4, IL-5, IL-17, and IFN), AMPK activation-dependent aspirin and statins (inhibiting inflammatory events: NFκB, mTOR, PGE2, HIF, *etc.*), oral anticoagulants, PAR-2/4 antagonist, and complement inhibitors (suppressing coagulation-triggered inflammation, HMGB1 release, *etc.*), PPAR agonists (downregulating NFκB/AP-1/NFAT, shifting to MΦ M2 polarization, *etc.*), PDE4 inhibitors (downregulating NFκB, TNF release, *etc.*), *etc.*

4.3 Anti-CVD

CVD, a non-communicable disease, presents a group of disorders of the heart (e.g., HF, MI, hypertrophy, arrhythmia including atrial fibrillation (AF), *etc.*) and blood vessels (vascular diseases: e.g., atherosclerosis, hypertension, and thrombosis). HF, cardiomyopathy, and cardiac arrhythmia often involve increased [Ca2$^+$]i and abnormal myocyte Ca2$^+$ signaling, while cardiomyocytes apoptosis mediates HF. Lack of cardiac energy involving defects in substrate (e.g., fatty acid, glucose) utilization, mitochondrial oxidative phosphorylation, and ATP transfer also plays a contributing role, being recognized as a chemical nature of HF. The interplays among different major CVD types (atherosclerosis, MI, cardiac hypertrophy, arrhythmia, AF, HF) forming feed-forward loops make CVD so complicated. As a metabolic syndrome, CVD significantly overlaps with other members including diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD), exhibiting diverse risks and complexity. For instance, obesity and diabetes have hiked recent CVD rate; otherwise, CVD has been trending down during late 20th and early 21st century [146,147].

CVD common risks include oxidative stress, CVD features (hyperlipidemia: hypercholesterolemia, hypertriglyceridemia, and elevated Lp[a]; endothelial dysfunction: elevated ET-1, reduced NO and PGI2, ele-

vated AT-II; thrombosis: hypercoagulation, platelet activation/aggregation, hypofibrinolysis; hypertension; hyperhomocysteinemia), and other risks including inflammation, diabetes, and obesity.

4.3.1 Roles of Oxidation and Inflammation in CVD

(a) ROS initiates and progresses CVD. (*i*) ROS has been proposed to mediate arrhythmia, while NOX plays a role in AF. (*ii*) ROS activates NFκB and favors hypertrophic gene program. (*iii*) ROS can promote the initiation of coagulation by targeting the tissue factor (TF)-FVII complex. (*iv*) ROS also inhibits the production of natural anticoagulant APC, thus favoring coagulation and formation of thrombin and thrombus. (*v*) ROS is a known factor for endothelial dysfunction. (*vi*) Classical lipid hypothesis proposes lipid in the form of LDL accumulating in the intima; LDL-C is not only a classical biomarker, but also a risk factor and driver. LDL particle containing over 80% cholesterol and esters is oxidized. The uptake of OxLDL by MΦ CD36 scavenger receptor is not subject to cholesterol homeostasis; OxLDL activates PPARγ to stimulate its own uptake. OxLDL including oxidized PC activates ROS generation, thereby promoting actin polymerization. As a result, foam cells are immobilized and trapped in the intima [100,148]. Interestingly, OxLDL stimulates NOX [7,148]; therefore, it establishes a forward-feed loop of oxidative stress refueling atherogenesis. AT II *per se* induces NOX and mitochondrial-derived ROS [149] in VSMCs, directly linking hypertensive risk to lipid oxidative stress (OxLDL) in atherogenesis [100]. Atherogenesis typically features such OxLDL uptake, which is the hallmark for foam cell formation in the intima (phase I, fatty streak formation in the vascular lumen), which continues with phase II of fibrous plaque formation involving various cell adhesion followed by phase III of plaque rupture involving inflammation and matrix turnover. Severe atherosclerosis will lead to MI progressing as congestive heart failure. (b) Atherosclerosis is a chronic inflammatory disease [150,151]; inflammation sets in and results in monocyte adhesion followed by penetration into endothelial layer, and leukocyte recruitment by rolling and adhesion. Various inflammatory signals activate VSMC, EC, *etc*. (*i*) Not only does inflammation set in atherogenesis, but also OxLDL *per se* in the intima is proinflammatory including the stimulation of expression of TNF, CRP, VCAM, ICAM, MCP-1, E-selectin, *etc.*, all of which facilitate VSMC proliferation, fibrous cap formation, *etc*. (*ii*) Saturated fats and accumulated intracellular cholesterol crystals are proinflammatory, which activates inflammasome NLRP3 that in turn leads to procaspase-1 activation, thereby consequently maturing pro-IL1β/18 for their secretion. NLRP3 activation also leads to pyroptosis, an inflammatory cell death. Such positive feedback loops of inflammation result in severe atherosclerosis that could lead to MI possibly followed by congestive heart failure [152,153]. (*iii*) Furthermore, other risk factor such as ATII

or CD40/D40L driving the "ROS-inflammation axis" [95–100] readily encourages CVD development.

4.3.2 Pharmacological Prevention and Treatment of CVD

A growing list of innovative treatments (US-FDA approved drugs) are available for CVD. (a) For hypolipidemic actions, statins, ezetimibe, ApoB100 inhibitor, ApoC3 inhibitors, PCSK-9 inhibitors/mAb, bile acid sequestrants, hypoTG agents or LPL up-regulators (ApoC2 and ApoA5 activators and ApoC1/3 (ISIS 304801) inhibition), ANGPTL3/4 blockade (anti-ANGPTL3 mAb (evinacumab; REGN1500), anti-ANGPTL4 mAb (REGN1001)), microsomal triglyceride transfer protein (MTP) inhibitor (lomitapide/implitapide), and fibrate derivatives (e.g., bezafibrate), and Apo[a] lowering agents (ISIS-Apo(a)Rx and PCSK-9 inhibitors). (b) In anti-thrombosis approaches: aspirin, anticoagulants (e.g., anti-FXa, heparin, low molecular weight heparin (LMWH), and warfarin), tissue plasminogen (tPA) activators (e.g., streptokinase, urokinase, alteplase, reteplase, tenecteplase, anistreplase, desmoteplase, or viprinex), and antiplatelet agents (aspirin, clopidogrel, prasugrel, dipyridamol, abciximab, cilostazol, and ticagrelor as well as ADP receptor inhibitors (ticagrelor, prasugrel, clopidogrel, or cangrelor) are often employed. In addition, TM5007 [154] inhibits PAI-1 activity, while TAFI inhibitors [155] include guanidinoethyl-mercaptosuccinic acid, ϵ-amino caproic acid, potato tuber carboxypeptidase inhibitor, DL-2-mercapto methyl-3-guanidinoethyl-thiopropanoic acid, leech carboxypeptidase inhibitor, tick carboxypeptidase inhibitor, SAR-104772, compound-8/14, UK-396,082, AZD-9684, BX 528, EF6265, *etc*. (c) Anti-hypertension approaches involve drug combinations (renin inhibitor/calcium-channel blocker, AT_1R antagonist/diuretic, AT_1R antagonist/calcium-channel blocker, AT_1R antagonist/calcium-channel blocker/diuretic, or calcium-channel blocker/renin inhibitor/diuretic), RAAS-targeting diuretics (e.g., hydrochlorothiazide), β-blockers, ACE inhibitors, AT-II inhibitors, rennin inhibitors, AT-II receptor blockers, $Ca2^+$ channel blockers (e.g., amlodipine), α-blockers, and α/β-blockers. PDE5 inhibitors (sildenafil and vardenafil), PGI2 analogues (epoprostenol or iloprost), vasodialator (andrenomedullin), *etc*. (d) In view of inflammation elevating Lp[a], anti-IL-6 mAb (tocilizumab) delivers efficiacy in treating atherosclosis by blocking LPA promoter activity, thus suppressing hepatic apo[a] expression and Lp[a] synthesis. STAT3/JAK2 inhibitor (WP1066) also diminishes IL-6-induced LPA promoter activity. (e) Others such as amiodarone and dronedarone are effective, while β-blockers, digoxin, ACE inhibitors, and AT receptor blockers are classical treatments for anti-arrhythmia.

4.3.3 Polyphenolic Actions

(a) Fig. 2 predicts that polyphenols offer a host of benefits to CVD, suppressing CVD features by antagonizing hyperlipidemia, thrombosis, hypertension, and hyperhomocysteinia (please refer to 4.3.3.1 to 4.3.3.4). (b) Improved EC function (e.g., anti-hypertension, reduced PAI-1/2, ET-1 attenuation, and ACE inhibition), hypolipidemic effects (please refer to 4.3.3.1), anti-oxidation (please refer to 4.1.3), antiinflammation (please refer to *4.2.3*), and anti- hypertensive and thrombotic events readily fight against atherosclerosis, MI, and HF. (c) For protection from hypertrophy, polyphenols alleviate its pathogenesis by FOXO upregulation (atrophic gene: atrogin-1 expression), PI3K/AkT/mTORC1 inhibition (please refer to 3.3 (*22*)), β-catenin inactivation (please refer to 3.3 (*23*)), and downregulated $[Ca2^+]i$ (please refer to 3.2 (*7*)) and its consequent calcineurin-dependent NFAT activation. The exhibited EC-dependent or independent VSMC relaxation and improved EC functions attenuate hypertrophy. (d) The abilities to inhibit ACE (please refer to 3.3 (*30*)), PDE (please refer to 3.3 (*32*)), blood coagulation (please refer to 3.3 (*35*)), PAI-1 production (please refer to 3.4 (*43*)), and platelet aggregation (please refer to 3.2 (*7*) & (*11*)) along with K^+ channel activation (please refer to 3.4 (*41*)) and the classical anti-oxidative potentials (please refer to 4.1) are capable of combating fibrosis and arrhythmia and its manifestation (e.g., AF and angina).

4.3.3.1 Hypolipidemic Actions. Polyphenol-induced AMPK activation mediates hypolipidemic effects including suppressed lipogenic transcription factors (e.g., SREBP1/2, C/REBP, *etc*.) (please refer to 3.2 (*16*)) and enzymes (e.g., HMG-CoA reductase, acetyl-CoA carboxylase, *etc*.) (please refer to 3.2 (*7*)) for *de novo* biosyntheses of cholesterol and fatty acids as well as TG formation. Concerning hypertriglyceridemia with elevated circulating TG level, polyphenols lead to LPL upregulation and suppressed ANGPTL4 mRNA expression (please refer to 3.2 (*19*)). LPL is a key enzyme responsible for TG degradation in TG-rich VLDL particles, while ANGPTL4 inhibits LPL activity. Thus, polyphenols present hypo-TG action.

4.3.3.2 Anti-Thrombosis. (a) Polyphenols' anticoagulation (inhibition on FXa, thrombin, *etc*.; please refer to 3.3 (*35*)), hypofibrinolytic (e.g., downregulated PAI-1, upregulated tPA; please refer to 3.4 (*43*) & (*44*)), and anti-platelet functions (suppressed TxA2, P-selectin, *etc*.) readily contribute to anti-thrombosis. (b) AMPK-dependent eNOS activation (please refer to 3.2 (*10*)) in turn enhances NO bioavailability for protecting platelets from activation and aggregation. In addition, the classical antioxidative potentials also improve EC function and NO bioavailability. (c) The anti-inflammatory potentials interrupt the coagulation-thrombosis-inflammation circuit [103–106], showing anti-

thrombosis. (d) NFκB inactivation (please refer to 3.2 (*11*)) and consequent COX inhibition result in TxA2 suppression, which is also in line with anti-platelet.

4.3.3.3 Anti-Hypertension.
(a) ACE inhibition targets RAAS and AT-II-induced oxidative stress, sGC inhibition, and ET-1 elevation (please refer to 3.3 (*34*)), largely presenting anti-hypertension. (b) Improved EC function (e.g., reduced ET-1/ROS, enhanced NO bioavailability, and PGI2) exhibits EC-dependent relaxation, while direct K^+ channel activation (please refer to 3.4 (*41*)) and PDE inhibition (please refer to 3.3 (*32*)) result in EC-independent vasodilation.

4.3.3.4 Anti-Hyperhomocysteinemia.
Although limited information is known about the direct effects on homocysteine level, the diverse polyphenolic actions could be expected to significantly counteract hyperhomocysteinemia consequences.

It is also noted that polyphenols readily exhibit antagonisms against known CVD risks: inflammation, diabetes, and obesity, all of which are elucidated and summarized in this review. It is not surprising that clinical trials have revealed polyphenolic actions in combating hyperlipidemia (elevated cholesterol, LDL, and TG), hypertension (vasoconstriction, elevated ATII, ET-1, and ROS), atherosclerosis-MI-HF axis (hyperlipidemia, oxidative stress, inflammation, hypertension, thrombosis, platelet aggregation, *etc*.), thrombosis (platelet aggregation, hypercoagulation, hypofibrinolysis), hypertrophy (oxidative stress, hypertension, inflammation, *etc*.), arrhythmia (oxidative stress, fibrosis, channel defects, *etc*.), AF (arrhythmia, hypertension, thrombosis, *etc*.), ischemia/reperfusion (oxidative stress, $Ca2^+$ overload, MI, metabolic acidosis, inflammation, *etc*.), and angina (AF, plaque, blocked flow, ischemia, *etc*.) [156].

4.4 Anti-Diabetes

Both autoimmune insulin-dependent diabetes I and insulin-resistance diabetes II feature hyperglycemia and elevated AGE (HbA1c), a monitoring system for stable blood glucose level, *per se* promoting diabetes progression. AGE signaling promotes oxidative stress and inflammation, in turn feedforwarding and refueling diabetes exacerbation in a vicious cycle. Inflammatory AGE signaling through its receptor (AGER) is analogous to TLR4 signaling, posing multiple health threats. In view of the ability of AGE to induce oxidative stress and inflammation for triggering many pathological manifestations, it is not surprising that diabetes is associated with diverse complications. (1) Hyperglycemia readily induces oxidative stress, inflammation, AT II formation, EC dysfunction, thrombosis, vessel calcification, *etc*. all of which lead to the development of diabetic microvascular complications. AGE promotes calcification, a condition of blood vessel stiffness, as CVD risk

associated with atherosclerosis and hypertension as well as thrombosis, for instance. (2) Diabetes is known to associate with multiple electrolyte disorders, which consequently poses its closely associated risk of acid-base imbalance (i.e., ketoacidosis, ketone body overproduction). Ketoacidosis and its treatment are often associated with brain edema. (3) Diabetes I & II present increased risk for bone fragility; increased osteoclastogenesis and suppressed osteoblastogenesis favor osteoporosis. (4) Diabetic peripheral neuropathy is one of the most common forms of neuropathic pain, with its incidence set to increase as the obesity and diabetes epidemics continue to grow, which is largely mediated by damage to the microvasculature that supplies nerve fibers, blocked or damaged blood vessels causing damaged nerve fiber. (4) Diabetes including diabetes I often induces and exacerbates steatohepatitis, chronic viral hepatitis, and end-stage liver disease (cirrhosis and hepatocellular carcinoma). (5) Diabetic macular edema, retinopathy, and nephropathy and impaired wound healing have been observed and reported. (6) Diabetes insipidus associated with defect antidiuretic vasopressin release exhibits increased urine flow and excess thirst/drinking. (7) Diabetes II is often associated with hypoTH.

4.4.1 Roles of Oxidative Stress and Inflammation in Diabetes

(a) Hyperglycemia, through various mechanisms, *per se* leads to increased ROS production. Excessive ROS can feedback and contribute to the pathogenesis of insulin-resistance and impaired insulin secretion, not to mention about the oxidation-inflammation axis [95–100] in diabetes initiation and progression. (b) Inflammation confers insulin resistance. Inflammation, cytokines (IL-1β, IL-6, TNF, IFN), and metabolic stress are capable of inducing β cell apoptosis mediated by IRS-2 ubiquitination, exhibiting insulin deficiency in diabetes II. Hyperglycemia and hyperlipidemia lead to insulin resistance and β cell apoptosis, which is consistent with the notion that obesity likely develops diabetes II. (*i*) In fact, AGE *per se* is inflammatory; hyperglycemia with elevated AGE that induces EC apoptosis, iNOS, and COX-2. AGE signal transduced through its receptor (RAGE) is similar to TLR-dependent cytokine signaling, which activates inflammatory kinase JNK or IKK and in turn blocks IRS tyrosine phosphorylation, leading to insulin resistance. In addition, diabetes as manifestation of obesity receiving adipocytokines (e.g., TNFα, IL-6, leptin, *etc*.) leads to insulin resistance. (*ii*) Proinflammatory cytokines encourage insulin resistance by activating suppressor of cytokine signaling-3 (SOCS-3). SOCS-3 directly binds insulin receptor and blocks the receptor recognition of IRS, thus suppressing signaling initiation. SOCS-3 is also able to bind IRS and function as E3 ligase, inducing IRS degradation and reducing insulin signaling. (*iii*) A nonreceptor-type phosphotyrosine phosphatase (PTP1B) dephosphorylates the receptor, limiting its activity. How-

ever, the receptor auto-phosphorylation and signaling produces H_2O_2 that inhibits PTP1B, leading to prolonged insulin signaling. (*iv*) An SH2-containing adaptor protein, Grb10, binds and inhibits the receptor kinase activity. Recently, mTORC1 has been shown to phosphorylate and enhance the inhibitory effect of Grb10 on the receptor. (*v*) Serine/threonine kinases (e.g., JNK or IKK) phosphorylate IRS in response to proinflammatory cytokines and thus inhibit the recognition of IRS proteins by the receptor tyrosine phosphorylation. Namely, inflammation (e.g., IL-6 or TNF) through its corresponding receptor autophosphorylation activates JNK1 and STAT3 that in turn facilitates IRS serine phosphorylate to compete with IRS tyrosine phosphorylation of initiating insulin signaling. Similarly, TLR-mediated IKK activation in response to inflammation competes with IRS tyrosine phosphorylation to block insulin signaling [157].

4.4.2 Common Anti-Diabetes Therapeutic Strategies

Several common anti-diabetes strategies have been reported [158]. (a) Sulfonylurea binds and closes K^+ channels for β cell depolarization and insulin granule secretion. (b) Na^+/glucose symport inhibitors (e.g., dapagliflozin, canagliflozin and empagliflozin) block glucose reuptake/reabsorption from urine during Na^+ recovery from the kidney, lowering blood glucose level for a better glycemic control. (c) GLP-1 analogs (exenatide and liraglutide)/GLP-1 receptor agonists (liraglutide, semaglutide, lixisenatide, and once-weekly extended-release exenatide)/GLP-1 ligands mainly promote insulin secretion. GLP-1 released in response to ingestion of nutrients essentially acts on pancreatic β cells to stimulate insulin secretion. Through GLP receptor, GLP-1 activates adenylate cyclase causing increased levels of intracellular cAMP and activation of PKA. As a consequence, PKA activation closes K^+ channel causing $Ca2^+$ influx for insulin secretion from β cells. In addition, (*i*) GLP-1 activates AMPK, mediating insulin sensitivity via eNOS phosphorylation and activation for Glut-4 translocation and resulting in enhanced glucose utilization by peripheral tissues (muscle, adipose tissue, liver, heart, *etc*.); (*ii*) GLP-1 inhibits glucagon release from α cell; and (*iii*) GLP-1 receptor activation and its downstream EPac2 recruitment to membrane (increased cAMP) cause natriuretic peptide secretion from atrial cardiomyocytes; natriuretic peptide also stimulates glucose-stimulated insulin secretion. (d) DPP-4 inhibitors (e.g., gliptins, saxagliptin, alogliptin, and sitagliptin) prevent GLP-1 rapid degradation by DPP-4. (e) In addition to AMPK activation, metformin inhibits cAMP production, blocking the action of glucagon, and thereby reducing fasting glucose levels. Metformin also induces a profound shift in the microbiota profile that may contribute to its mode of action possibly through an effect on GLP-1 secretion. Apart from suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (inducing the phosphorylation of GLUT4 enhancer factor), decreases insulin-induced suppression of fatty acid oxidation, and decreases the absorption of glucose from the GI tract. Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors. (f) Thiazolidinediones (PPAR-γ agonists; e.g., rosiglitazone) increase storage of FFAs (carbohydrate utilization) in adipocytes, thus decreasing circulating glucose levels. (g) Basal/long lasting -insulin replacement supplements insulin and β cell death-induced insulin deficiency in diabetes I and II, respectively.

4.4.3 Polyphenolic Actions

(a) Polyphenols mimic/reinforce insulin action: (*i*) AMPK-mediated eNOS activation (please refer to 3.2 (*10*)) increases glucose uptake/utilization through Glut-4 translocation. (*ii*) AMPK induces adiponectin elevation (please refer to 3.2 (*21*)) and increases GLP-1 production. GLP-1 and its ligand promote insulin secretion without weight gain. (*iii*) PI3K/AkT inhibition (please refer to 3.3 (*22*)) accompanying with JNK inhibition (please refer to 3.3 (*29*)) leads to suppressed insulin resistance and resulting mTORC1 inhibition promotes glycolysis (glucose utilization). (b) α-Glucosidase inhibition (please refer to 3.3 (*31*)) reduces glucose inputs from dietary carbohydrates, certainly lowering glycemic index. (c) Recent insights reveal that flavonoids promote proliferation and reducing apoptosis of pancreatic β-cells. (d) As prebiotics (please refer to 3.4 (*47*)), polyphenols could alter gut microbiota, which contributes to energy harvesting from diets, satiety, insulin sensitivity, *etc*.

Diverse antagonisms against the initiation (please refer to 4.4.1 (a) (b)) and pathophysiology (please refer to 4.4.1) of diabetes by polyphenols (Fig. 2) are compatible to common pharmacological approaches (please refer to 4.4.2 and Table 1) including GLP-1/GLP-1L analogs/mimetics (AMPK activation, K^+ channel closure, $Ca2^+$ influx, increased insulin release, eNOS activation, *etc*.), AMPK-dependent metformin (depressed hepatic gluconeogenesis, shifting microbiota profiles, *etc*.), *etc*.

4.5 Anti-Obesity

Obesity features chronic low-grade inflammation, excessive food intake, and energy surplus in addition to genetic factors (e.g., melanocortin 4 receptor (MC4R), leptin deficiency). Obesity is a major risk factor for non-communicable diseases (e.g., diabetes II, hypertension, dyslipidemia, CVD, cancers, *etc*.). Hyperlipidemia *per se* in obesity lead to insulin resistance and β cell apoptosis, which is consistent with the notion that obesity likely develops diabetes II. For instance, lipid overload (obesity) promotes insulin resistance (diabetes II) also known as diabesity via (1) proinflammation, (2) insulin receptor internalization by resistin, (3) ER stress, (4) leptin deficiency, and (5) exosomal miR155 that is secreted by proinflamma-

tory M1 MΦs in adipose tissue. It is also noted that obesity as risk factors for pancreatitis, pancreatic cancer, and iron deficiency anemia induces NAFLD (overproduction of hepatic VLDL-TG). A growing list of its pathologies could include neuropsychiatric disorders (dementia, depression and anxiety).

4.5.1 Roles of Oxidative Stress and Inflammation in Obesity

(a) Obesity is known as a low-grade inflammatory disease [159–162], although it is not proposed that inflammation is an initial cause of obesity. Adipose tissue is a large endocrine system; adipocytes produce a variety of biologically active molecules known as adipocytokines or adipokines, including PAI-1, visfatin, resistin, leptin, and adiponectin in addition to TNF-α, IL-6, MCP-1, and others. Metabolically, FFAs activate TLR-4 and excessive cellular ATP triggers inflammsome (NLRP3) activation, contributing to inflammation. Moreover, obesity *per se* drives MΦs into M1 polarization that is characterized by iNOS and further produces TNFα, IL-1β, IL-6, MCP-1, and $O_2\bullet^-$[162]. (b) In addition, increased ROS/RNS and ROI/RNI in obesity readily refuel chronic inflammation. (*i*) During adipogenesis (differentiation of adipogenic precursor cells (i.e., preadipocytes) into adipocytes), activated NOX and increased mitochondrial biogenesis with complex I/II/III impairment readily result in excessive ROS production [163,164]. (*ii*) Consistent with such notion, Nrf2 and antioxidant enzyme (SOD2, catalase, GSH-Px) expression are upregulated in response to the increased ROS in obesity [165]. Nrf2 then induces C/EBPb followed by turning on C/EBPα and PPARγ, both of which in concert are master genes for terminal adipogenesis [163,164]. (*iii*) Apart from such intracellular ROS, extracellular redox state triggering intrinsic ROS production could further promote adipogenesis.

4.5.2 Common Anti-Obesity Therapeutic Strategies

The classical approaches include (a) Orlistat (Xenical) inhibits pancreatic lipase, lowering dietary fat absorption; (b) serotogenic drugs (sibutramine) suppress appetite; other incretin mimetics or analogues fluoxetine and sertraline in the treatment of depression such as (S)-fenfluramine, fluoxetine, and sertraline are developed for satiety reducing food intake; (c) classical CCK mimetics (non-peptide benzodiapine and its derivative with indazole substitutions) block CCK signaling for food intake; (d) thermogenic drugs (Bisphenyl ethylamines (BRL 35135), triphenyl ethylamine (CL 316243), RO 40-2148, and [(S)-4(2-(hydroxyl-3-phenoxy propyl) amino)ethoxy]-N-(2-methoxyethyl)phenoxy acetamide (ZD 7114), a 1,4-dioxybenzene compound) increase thermogenesis burning fat in brown adipose tissues, thereby gradually reducing body fat; (e) naltrexone/bupropion combination enhances POMC-mediated release of MSH for reduced food intake

and increased energy expenditure; (f) an MC4R agonist (setmelanotide) could be for weight loss, while amylin mimetics, leptin analogues, ghrelin antagonists, GLP-1 analogues, GLP-1 agonist (liraglutide), and NPY antagonists are also of anti-obesity in pre-clinical trials, showing promising results; and (g) bariatric surgery (e.g., gastric pouch reduction/bypass, Roux-en-Y gastric bypass) remains clinically effective by decreased ghrelin production; it also benefits to anti-diabetes by activating GLP-1 expression.

4.5.3 Polyphenolic Actions

(a) The classical polyphenolic anti-oxidative stress (please refer to 3.1 (*1*) to (*6*) and 4.1) certainly blocks ROS-mediated inflammation [95–100], a common pathogenesis of obesity. (b) Polyphenols' hypolipidemic effects (please refer to 3.2 (*7*), (*13*), (*16*), *etc*.) also account for anti-obesity; accordingly, polyphenols reduce adipogenesis. (c) The AMPK activation-mediated consequence of SirT1 activation (please refer to 3.2 (*8*)) ensures the inhibitions on the genes involved in adipocyte differentiation and TG accumulation. (d) AMPK activation favors shifting MΦ M1 to M2 polarization (please refer to 3.2 (*7*)); proinflammatory M1 polarization in white adipose tissues is one of obese characteristics. (e) Suppressed ADD1/SREBP-1c signals (please refer to 3.2 (*16*)) are associated with decreased levels of PPARγ as well as C/EBP α/δ mRNA levels during adipogenesis resulting from mTORC1 inhibition [22,37]. Inactivation of PPARγ, a known master gene for adipogenesis and adipocyte differentiation, thus blocks adipogenesis, lipogenesis, and fat accumulation, contributing to anti-obesity [22,37]. (f) PPARγ and C/EBP α/δ inactivation (please refer to 3.2 (*17*)) also result from β-catenin inactivation independently of AMPK. (g) The AMPK-mediated adiponection elevation (please refer to 3.2 (*21*)) leads to food-intake suppression and weight loss in addition to antiinflammation. For instance, grape resveratrol increases serum adiponectin and downregulates inflammatory genes (*PAI-1, IL-6, AP-1, JUN, CREBP, etc*.) [42]. 7-O-galloyl-D-sedoheptulose increases adiponectin level while downregulating leptin, insulin, C-peptide, resistin, TNFα, and IL-6 in serum and proinflammatory NFκB p65, COX-2, iNOS, JNK, phospho-JNK, AP-1, TGFβ1, and fibronectin [43]. Green tea extract upregulates adiponectin and its signaling, promoting BAT thermogenesis accompanied by decreasing final BW gain, adiposity index, adipocyte size and insulin resistance, induced energy expenditure, and promoted fat browning in animal models [166]. (h) As prebiotics (please refer to 3.4 (*47*)), polyphenols could alter gut microbiota with suppressed "obese microbiota". However, it remains largely unknown whether polyphenols affect satiety, incretins, and food intake involving regulations on neuronal pathways.

Exception from genetic factors, polyphenols could offer a broad spectrum of anti-obesity. Antagonisms

against the adipogenesis/risk (please refer to 4.5.1 (a) (b)) and pathophysiology (please refer to 4.5.1) of obesity by polyphenols (Fig. 2) are similar to common pharmacological approaches (please refer to 4.5.2 and Table 1) including thermogenic drugs that mainly suppress energy production. Polyphenolic anti-diabetes actions (please refer to 4.4.3) also extend to anti-obesity concerning GLP-1/GLP-1 analogs/mimetics (please refer to 4.5.2 and Table 1).

4.6 Anti-Cancers

Oxidative stress and inflammation play major roles in tumorigenesis and progression; oxidation-inflammation axis [95–100] further ensures cancer initiation and activities ranging from proliferation, angiogenesis, stemness, *etc*. to metastasis, all of which fall into cancer hallmarks.

4.6.1 Hallmarks of Cancer

Cancer is characterized with multiple cellular malfunctions. The major cancer hallmarks include sustained proliferative signaling, evaded growth suppressors, resistance to cell death, replicative immortality, induced angiogenesis, activated invasion and metastasis, epigenetic dysfunctions, reprogrammed energy metabolism (e.g., Warburg effect, serine consumption, glycine uptake, *etc*.), and escaping immune destruction in addition to uncontrolled signaling upregulations. Tumor immunosuppressive microenvironment simply allows immune silencing and encourages T cell inactivation, further supporting cancer stemness, survival, and progression.

4.6.2 Roles of Oxidative Stress and Inflammation in Cancer

(a) Oxidative stress ensures tumorigenic progression. Activated oncogenes could promote ROS production; the resulting DNA damage leading to genomic instability and mutations plays a major role in cancer initiation [7,101, 167–170]. Further, the notion that tumor suppressors (e.g., p53, FOXO, retinoblastoma, p21, and p16,) act as antioxidants consistently supports the role of ROS in tumorigenesis [171]. It is also well established that ROS induces HIF1α, contributing to angiogenesis and metastasis. (*i*) Concerning DNA damages, purine nucleoside oxidation by OH• to form 8,5'-cyclo-2'-deoxyadenosine. Similarly, 8,5'-cyclo-2'-deoxyguanosine will result from deoxyguanosine interaction with OH•. As a result, the radical derivatives significantly induce gene mutations and alter gene transcriptions. In addition, H abstraction of deoxyribose leads to single strand breakage, while activation of endonuclease cleaves phosphodiester bond triggering DNA fragmentation [7,101,167–170]. OH• damage to pyrimidines is also mutagenic. 5-Hydroxydeoxycytidine (5-hydroxy-dC) induces C→T and C→A mutations in vitro and C→T transitions *in vivo*. 5-Hydroxy-dC also deaminates to 5-hydroxy-deoxy-uracil, which codes as T. This provides an additional mechanism for the induction of C→T transitions. Thymidine glycol causes T→C mutations *in vivo*. Furthermore, DNA adducts with lipid peroxidation products, making more damaging DNA modification [172]. Interestingly, independent of excessive UV radiation, apart from UV exposure, endogenous pheomelanin is considered as an intrinsic carcinogen (intrinsic source of ROS), leading to DNA lesion driving melanoma [173]. Clinically, elevated pheomelanin level often associated with "red-hair" susceptible to melanoma also links to high frequency in BRAF V600E mutation, which suggests pheomelanin and the BRAF mutation together readily posing threats to melanoma risk in an UV-free environment. (*ii*) Tobacco smoking remains a major health risk not only limiting to lung cancer. Tobacco burning generates RNS/RNI to proceed with radical chain-reactions. For instance, deoxyguanine (dG) undergoes nitration by ONOOH or ONOOCOO$^-$ to form unstable adduct 8-nitro-dG leading to DNA strand cleavage. 8-nitro-dG further reacts with ONOOH, resulting in 8-oxo-dG for mutation induction. In addition to single strand breakage, N_2O_3 readily reacts with dA/C/G forming diazo intermediates that are further hydrolyzed to hypoxanthine, uracil, and xanthine, causing mispairing and G→A/T mutation [174]. (*iii*) Concerning oxidation-inflammation axis of forward feeding loop, oxidative stress readily provides a tumorigenic momentum. (b) Inflammation certainly plays crucial roles in every phase of tumorigenesis including cancer initiation, promotion, and progression [175,176]. Diverse damaging cytokines and chemokines produced by immune cells during inflammation readily trigger signaling cascades and cell proliferation/differentiation. Inflammation essentially represents a link between intrinsic (e.g., oncogenes, tumor suppressors, and genome stability genes) and extrinsic (e.g., immune and stromal components) factors contributing to tumor development [177]. (*i*) Inflammatory cells initiate cancer development. ROS/RNS/RNI produced by inflammatory cells promotes mutagenesis, causing mutations in neighboring epithelial cells. Also, cytokines produced by inflammatory cells can elevate intracellular ROS/RNS/RNI in premalignant cells. In addition, inflammation upregulates NFκB and activation-induced cytidine deaminase, leading to genomic instability and epigenetic changes that favor tumor initiation. Moreover, STAT3 activation encourages stem cell reprogramming/renewal, while NFκB activation facilitates survival and antiapoptosis by upregulating Wnt/β-catenin pathway, for instance, for colonic tumor growth. It is also noted that oncoproteins (e.g., Ras, MyC, *etc*.) of initiated tumor induce inflammatory cytokine (IL-6/8/1β) and chemokine (CCL2/20) production as a positive feedback loop, ensuring tumor-associated inflammation to contribute to further ROS, RNI, and cytokine production [175,176]. (*ii*) Inflammation readily prompts cancer progression. Proinflammatory cytokines (e.g., TNFα, IL-23) produced by tumor-infiltrating immune cells activate key transcription factors (NFκB or STAT3) in premalignant cells to control

numerous pro-tumorigenic processes in a paracrine fashion, promoting premalignant cells to a primary tumor. As parts of positive feed-forward autocrine loops, NFκB, AP-1, and STAT3 activations induce production of chemokines that attract additional immune/inflammatory cells to sustain autocrine tumor-associated inflammation, leading to survival/antiapoptosis, proliferation, growth, angiogenesis, and invasion [175–177]. (*iii*) Inflammation enhances angiogenesis as the result of NFκB, STAT3, and AP-1 activations and proangiogenic factors such as angiopoetin2, VEGF, IL-8, CXCL-1/8, including HIFα expression all being upregulated [176,177]. (*iv*) Inflammation also encourages cancer metastasis. Inflammation engages in every steps of metastatic process. Mechanistically, TNF signaling represses E-cadherin transcription; the loss of E cadherin increases tumor motility for invading epithelial layer and basal membrane. Inflammatory prostaglandins or MMPs increases vascular permeability, allowing tumor cells' intravasation into blood circulation. In addition, chemokine receptors (CXCR4, CCR4/7/9/10) direct such intravasation. Inflammatory cytokines (e.g., IL-6, TNFα, and epiregulin) promote tumor cell's survival in blood circulation for micrometastasis and extravasation. Inflammatory extracellular matrix component: versican leads to MΦ activation and induces TNF production in MΦs, ensuring adhesion and metastatic cell attachment in a new landscape. Furthermore, inflammation derived from IL-1/6 and TNFα followed by NFκB and STAT3 activations promotes MMP expression for invasion. In addition, chemokine: CCL-9 induces MMP2/9 secretion [176,177] that contributes to metastasis, angiogenesis, migration, and beyond.

4.6.3 Pharmacologic Anti-Cancer Strategies

Cancer treatments remain most focused basic and clinical research. Classical cancer treatments include chemotherapies, radiation/surgery, and immunotherapies [178]. In addition to target/precision oncotherapies, many developing innovations include combinations of oral chemo- prevention/therapeutic agents with DC/DNA/mRNA vaccines, significantly enhancing immune responses (e.g., Th1 enrichment, CD8+ T infiltration, *etc.*) for arresting tumor growth. Small molecules (e.g., CA 170) are also developed for immune checkpoint blockade in addition to mAbs against PD-1/PDL-1 or CTLA-4. (a) Metformin, bexarotene, zoledronic acid and other bisphosphonates, COX inhibitors, aromatase inhibitors, and retinoid ATRA are of cancer chemoprevention. For instance, aspirin is known CRC chemoprevention, while aromatase inhibitors are breast cancer chemoprevention agents. (*i*) Metformin increases effector CD8+ T cell populations and resulting memory cells, but also increases MHC-I expression on tumor cells, increasing visibility to effector CD8+ T cells. (*ii*) Bexarotene inhibits apoptosis in T cells by increasing expression of BCL2. (*iii*) Zoledronic acid and other bisphosphonates increase phosphoantigens

in peripheral blood mononuclear cells and on cancer cells, resulting in activation of anti-tumor $\gamma\delta$ T cells. Zoledronic acid readily decreases populations of M2 MΦs and may re-polarize them to the anti-tumor M1 MΦs. (*iv*) COX inhibitors (aspirin, celecoxib, naproxen, and meloxicam) can reverse PGE$_2$ effects on increasing immunosuppressive Treg, MDSC, M2 MΦs, and even Th2. The inhibition also blocks the PGE2 effect on Wnt/β catenin signaling assembly for CRC development. (*v*) Aromatase inhibitors (letrozole) reduce Treg populations and increased Th1-cytokine release; estrogen is known to promote a Th2 cytokine profile and expand Tregs. (*vi*) Retinoid (all *trans* retinoic acid; ATRA) can differentiate MDSCs into immature DCs, which may account for its ability to enhance proliferation of both effector and memory CD8+ T cells. (*vi*) Preventive vaccines (e.g., HPV vaccine) receives clinical efficicay. (b) Common chemotherapies, mentioning a few, have been practiced across different types of cancers. Chemotherapy-induced oxidative stress reduces the rates of both the proliferation and the survival of cancer cells, resulting in response and shrinkage of tumor volume. Chemotherapy leads to senescent cells undergoing a permanent cell cycle arrest (antiproliferation). Some resistance to chemotherapies including MDR-efflux and toxicities have been reported. It is noted that combined chemotherapies with cancer vaccines achieve better outcomes and survival rates. (*i*) Inhibitors of the Wnt signaling FRP (Frizzled-Related Protein), Cer (cerberus), WIF1 (Wnt-inhibitory factor-1), and Dkk1 (Dickkopf-1) could downregulate Wnt signaling. (*ii*) Small molecule kinase inhibitors including ATP-competitive vs. non-ATP competitive and covalent vs. non-covalent inhibitors suppress kinase activities by differential fashions, providing some specificity and reversibility for inhibitory actions. For instance, non-Type I ATP-competivitive erlotinib (quinazoline analog), dasatinib (pyrimidine analog), suninib (urea analog), gefitinib (quinazoline analog) target VEGFR, EGFR, FGFR, PDGFR, KIT, FLT3, ABL1/2, SRC, RET, and CSFR; Type II ATP-competivitive imatinib (pyridine/pyrimidine analog), nilotinib (pyridine/pyrimidine analog), sorafenib (pyridine analog), vatalinib, lapatinib (quinazoline analog) could inhibit ABL-1/2, PDGFR, TIE2, MET, EGFR, VEGFR, PDGFR, BRAF, ABL-2, KIT, FLT3, PDGFR, Raf kinase, and ErbB2; non-ATP-competitive rapamycin analogs (everolimus and temsirolimus) apparently are able to suppress mTOR, CHK1, ABL, IKK, CDK2, and AkT. (*iii*) EGFR antagonists (e.g., Cetuximab & Panitumumab) are used as passive immunotherapy. (*iv*) Antagonism against AR and ER signaling includes inhibitions of steriodogenesis, AR/ER ligand-binding, DNA binding, coactivator binding, and AR/ER breakdown, thereby attenuating estrogen and androgen effects. For instance, aromatase inhibitor (anastrozole, letrozole), faslodex fulvestrant, tamoxifen, pyrrole imidazole polyamide, pyrimidines, guanylhydra-

zone, *etc*. attack ER signaling. Ketoconazole, abiraterone, finasteride, dutasteride, hydroxyflutamide, bicaltamide, pyrvinium maoate, polyamide, T3, flufenamic acid, T3 acetate, HDAC inhibitor, HSP90 inhibitor, *etc*. target AR signaling. (*v*) Bortezomib inhibits NF-κB, a central onco-gene associated with tumor proliferation/growth/migration, angiogenesis, EMT, and metastasis. (*xvii*) Fascin inhibits cell adhension. NFκB inactivation by IKKβ inhibitor (BMS-345541) could rescue resistance to tyrosine kinase inhibitors (erlotinib) in addition to its anti-metastasis. (*vi*) Doxorubicin, all-trans retinoid acid, TNF, and bisphos-phonates reduce telomerase activity by suppressing the expression of the catalytic RNA component. Antisense olgionucleotides to such telomerase RNA component suppress the expression and activity. AZT accelerates both apoptosis and telomere loss. (*vii*) Growth inhibition include apoptotic inducer, promoted phagocytosis by MΦs, antag-onism against inhibitor of apoptosis proteins (IAP), and inhibition of anti-apoptotic GAS6 (ligand)/AXL (receptor) pathway. (*viii*) Synthetic MMP inhibitors (doxycycline and chemically modified tetracyclines) inhibit the activity of MMPs, bevacizumab or VEGF inhibitors (sunitinib, pa-zopanib, and axitinib) targets VEGF and VEGFR, tyrosine kinase inhibitors (e.g., sorafenib or motesanib) supprerss VEGFR intracellular kinase activity, and AMG 386 targets Ang/Tie2 pathway all for anti- angiogenesis, invasion, tumorgenesis, and metastasis. (*ix*) For anti-hypoxia, aminoflavone inhibits HIF1α mRNA expression for the protein synthesis; mTOR inhibitors, cardiac glycosides, microtubule targeting agents, topoisomerase inhibitors, synthetic oligonucleotides, and PX-478 inhibit HIF1α translation and protein synthesis; HSP90 inhibitors, HDAC inhibitors, antioxidants, oligonucleotides, berberine, PX-12, and mTOR inhibitor/guanylate cyclase activator destabilize HIF1α protein; acriflavine blocks HIF-1α/β dimerization; anthracyclines, echinomycin, and doxoru-bicin block HIF1 DNA binding; and borterzomib inhibits HIF1 transactivation. (*x*) 5-FU (pro-drug capecitabine) inhibits thymidine synthase, presenting diverse impacts on pyrimidine, pruine, and one carbon metabolism along with elevated serum deoxyuridine/uridine represents overflow of nucleotide metabolism along with many other metabolic effects including decreased ATP/ADP and GSH/GSSG ratios and increased NADH/NAD$^+$ ratio in cancer cells. In addition, 5-FU attenuates glycolysis and decreases FA ox-idation, favoring anti-cancer. (*xi*) For restoring/enhancing immune responses, anti-CD47 Ab (CD47, a "don't eat me signal") is as effective as anti-PD-1/PDL1, anti-soluble NKG2D ligand mAB facilitates NK cell function in eliminating tumors, and IDO inhibitors (epacadostat) de-activates DMSC suppression. (*xii*) Small molecule THZ1 inhibits CDK7 for cell cycle proceeding. (*xiii*) High doses of vitamin C inhibits DNA demethylation; (*xiv*) PARP inhibitors (olaparib, AZD2281, ABT-888, BSI-201, KU-0058948, and AG-014699) promote DNA repair (cell cycle

arrest). (*xv*) Small molecule antagonists inhibit oncogenic pathways (PI3K/AkT/mTORC1, Ras/Raf/Mek/Erk, *etc*.). (*xvi*) For autophagy inhibition, 3-MA, BafA, LC3-RNAi, ATG5/7RNAi, ATG 3/4C/5/12-RNAi result in autophagy inhibition for treating glioma, myeloma, cervical, breast, colon, and prostate cancer treatments. Chloroquine and hydroxychloroquine blocking lysosomal acidification and indirectly inhibiting autophagy are under clinical trials of glioma, myeloma, cervical, breast, colon, lung (small cell or non-small cell), leukemia, multiple myeloma, and prostate cancer. (*xvii*) Trastuzumab and pertuzumab are the 2 current FDA-approved mAbs that inhibit the signaling of HER2 as target therapies. (*xviii*) Classical platinum-based (cisplatin, carboplatin, and oxaliplatin) treatment since 1978 basically restores DNA repair pathways. (*xix*) Taxol (paclitaxel) kills tumors by mitotic arrest across cancer types. Others such as sunitinib, temozolomide, gemcitabin, bortezomib, gefitinib, erlotinib, tamoxifen, *etc*. are also included in this chemotherapy category. (c) Immunothera-pies include active/passive immune modulations, adoptive T cells (ATC), CAR-T, CD8+ T activation, therapeutic DC/DNA/RNA vaccines, *etc*. (*i*) High dose IL-2 promotes T proliferation. (*ii*) PD-1/PDL-1 checkpoint blockade res-cues T exhaustion, while CLTA-4 Ab/inhibitor facilitates CD8+ T infiltration. (*iii*) CAR-T enhances cancer infiltrat-ing T. (d) Radiation therapy achieves efficacies in cancers such as prostate, brain, breast, lung, *etc*. Radiation therapy activates ATM that triggers p53 DNA repair mechanism and ROS production for killing tumors. (*i*) Radiation via ATM/ATR sensor induces p53 upregulation that elicits expression of CDK inhibitors to arrest cell cycle. (*ii*) ATM *per se* inhibits MDM2 (an E3 ligase) that degrades p53. (*iii*) ATM also phosphorylates Ser15 at N-terminus of p53, which facilitates dissociation with MDM2 resulting in p53 nuclear translocation. The resulting p53 effects favor apoptosis and suppresses cell proliferation. p53 inhibits Bcl-2 while enhancing the intrinsic apoptotic pathway in-cluding elevated cytoplasmic proapototic proteins (PIDD, Bid) and mitochondrial proapoptotic proteins: Bax, Bak, Puma, and Noxa. p53 also promotes the extrinsic pathway by elevating death receptors (Fas/Apo1, DR 5, *etc*.). (e) Surgery is often highly recommended at earlier stage of the treatment plan/sequence.

4.6.4 Polyphenolic Actions

In addition to the antioxidation and anti-inflammatory mechanisms by polyphenols, targeting specific tumori-genic signaling pathways/components certainly contributes to anticancer activities (Fig. 2), which has been generally demonstrated by (a) antioxidant activity scavenging free radicals (please refer to 3.1 (*1*)) and reducing oxidative stress, (b) inhibition of cell proliferation (e.g., NFκB inac-tivation, PKC inhibition, mTORC1 inhibition) (please refer to 3.3 (*26*), (*33*), (*36*)), (c) inhibition of cell differentiation (e.g., NFκB inactivation, PKC inhibition, *etc*.) (please re-

fer to 3.2 (*11*) & 3.3 (*36*)), (d) inhibition of oncogene (e.g., cMyC) expression (please refer to 3.3 (*26*)), (e) induction of tumor suppressor gene expression (e.g., p53, FOXO1, *etc*.) (please refer to 3.2 (*9*), (*12*), *etc*.), (f) induction of cell-cycle arrest, (g) induction of apoptosis (PKC inhibition (please refer to 3.3 (*36*)), (h) inhibition of oncogenic signaling pathways (IP3K/AkT/mTOR, JAK/STAT, *etc*.) (please refer to 3.3 (*22*), (*28*), *etc*.), (i) enzyme induction and enhancing detoxification: (e.g., Phase II enzyme: glutathione peroxidase, catalase, SOD), (j) enzyme inhibition (e.g., Phase I enzyme (blocked activation of carcinogens): COX-2, iNOS, xanthine oxidase) (please refer to 3.2 (*7*) & (*11*), 3.1 (*5*)), (k) enhancement of immune functions (please refer to 3.4 (*47*)) and surveillance (M2/Treg downregulation) (please refer to 3.1 (*7*), 4.2, *etc*.), (l) anti-angiogenesis (VEGF, TGFβ, NFκB inactivation, *etc*.) (please refer to 3.2 (*7*), 4.6.2 (b), *etc*.), (m) inhibition of cell adhesion and invasion (e.g., P-selectin), (n) suppressed metastasis (EMT, NFκB inactivation, *etc*.) (please refer to 3.2 (*11*) & 4.6.2, *etc*.), (o) reduced stemness (NFκB inactivation) (please refer to 3.2 (*11*)), (p) inhibition of nitrosation and nitration (please refer to 4.1 & 4.2 (c)), (q) prevention of DNA binding, (r) downregulation of steroid hormone metabolism and signaling, (s) downregulation of estrogen metabolism, (t) a target for attenuating cancers, β-catenin inactivation (please refer to 3.3 (*23*); curcumin blocking axin/APC/GSK3β/β-catenin complex disassembly for β-catenin degradation) by directly inhibiting GSK3β for quenching β-catenin release and nuclear translocation [28–30], also resulting in transcription factors: PPARγ and C/EBPα being downregulated (please refer to 3.2 (*17*)), (u) as epigenetic modifiers (please refer to 3.4 (*45*)), flavonoids, EGCG, genistein, resveratrol, and quercetin downregulating pro-cancer oncogene (e.g., *DNMT*, *HAT*, *HDAC*, *MECP2*, *etc*.) while upregulating acetylation and tumor-suppressor gene (e.g., *p53*, *SCUBE2*, *BRCA1/2*, *ERa/b*, *EZH2*, *p300*, *ATP2A3*, *etc*.) expression, and (v) anti-viral potentials (please refer to 4.8 (c)) reducing pathogenic risk.

Moreover, resveratrol and other dietary polyphenols are inhibitors of estrogen metabolism in human breast cancer cells. JAK/STAT1 inhibition by resveratrol [55] extends its benefit to IDO suppression for cancer immunoprotection; IDO plays roles in tumor immunosuppressive microenvironment. Resveratrol and other dietary polyphenols are inhibitors of estrogen metabolism in human breast cancer cells. Polyphenols also target HDAC 6-related pathways. Curcumin induces Nrf2 and increases the target gene HO-1 expression, favoring apoptosis with anti-tumor action. Polyphenols even target cell senescence or sphingolipid (ceramide)-mediated mechanisms, presenting novel cancer preventions and therapeutic strategies.

Antagonisms against the progression (please refer to 4.6.2 (a) (b), 4.6.4) and pathophysiology (please refer to 4.6.1) of cancers by polyphenols offer broad coverages compatible to current pharmacological approaches (please refer to 4.6.3 & Table 1) including chemoprevention (e.g., AMPK-dependent metformin & aspirin), target therapies (inhibiting PI3K/AkT/mTOR/ ERK/IKK/HIF/NFκB/AP1, suppressing JAK/STAT signaling, autophagy inducers, Th1 activation, Treg/Th17 downregulation, *etc*.), *etc*.

4.7 Anti-Neurogeneration

Neurodegeneration including AD, PD, HD, ALS, *etc*. generally involve neuro- peptide/protein accumulation that blocks neuro-transmission and functions. AD features toxic oligomeric Aβ protein accumulation, PD is characterized by α-synuclein aggregation/acummulation, and HD shows huntingtin protein overexpression/ aggregation with polyQ expansion. Interestingly, MS in the CNS could fall into this category, which is evidenced by white matter shrinkage/degeneration.

4.7.1 Roles of Oxidative Stress and Inflammation in Neurodegeneration

(a) Considering the role of oxidative stress in triggering neurodegeneration, largely deriving from activated microglia (resident MΦs) and astrocytes through NOX, ROS targets cholinergic or dopaminergic neurons and poses risks. (*i*) AD brain shows a decreased electron transport chain, especially decreased complex IV, thereby releasing ROS from mitochondria. AD is also reported with increased brain content of Fe2$^+$ and Cu2$^+$, both of which are capable of stimulating free radical formation. ONOO$^-$ induces tau protein hyperphosphorylation, nitration, and accumulation. Oxidative damage of lipids generates toxic aldehydes (4-HNE and MDA), leading to cholinergic neuron death. Interestingly, AGE *per se* could trigger ROS production from activated microglia, accounting for the risk by diabetes. (*ii*) Similarly, oxidative stress leads to PD pathogenesis. Mitochondrial damage has been associated with some PD incidence with deficit/impairment in mitochondrial complex I, resulting in reduced ATP production and enhanced free radical formation. Furthermore, there are reduced GSH and elevated iron in substantia nigra of PD patients. As a result, dopaminergic neuron apoptosis could occur. Environmental insults such as pesticides or insecticides are proposed to damage mitochrondria [179]. For instance, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine known as MPTP inhibits the complex I; the impaired/inhibited mitochondrial complex I leads to oxidative stress. Among which, particularly increase in 3,4-dihydroxyphenylacetaldehyde (DOPAL) is the critical endogenous toxin triggering dopaminergic neuron loss in PD. DOPAL reacts with H$_2$O$_2$ to generate OH• radicals triggering aggregation of toxic olgiomeric α-synuclein protein. The small acidic protein α-synuclein binds loosely to the surface of vesicles, possibly playing a role in synaptic dynamics and initiating dopaminergic neuron death. (*iii*) Concerning HD, ROS worsens the expansion of the CAG triplet repeat tract in postmitotic neu-

rons, resulting in a longer and more toxic polyglutamine expansion in huntingtin, with possible consequences on disease onset and progression. Interestingly, there is a positive feedback loop refueling ROS production. The mutant huntingtin protein suppresses activity of several enzymes involved in oxidative phosphorylation such as the complex I, II, III, and IV, leading to energy metabolism defects and enhanced ROS production. In addition, upregulated uncoupling protein 2 mRNA ensures inefficient coupling of electron transport to ATP production. (*iv*) Oxidative stress is also generally proposed to play a relevant pathogenic role in depression [180]. ROS and RNS have been demonstrated to modulate levels and activity of noradrenaline (norepinephrine), serotonin, dopamine and glutamate, all of which are principal neurotransmitters involved in the neurobiology of depression. Moreover, major depression has been associated with an impairment of the total antioxidant status with lowered endogenous antioxidants (vitamin E, zinc, and coenzyme Q10), or antioxidant enzymes (e.g., GSH-Px). (b) CNS inflammation as a risk factor, enormous amounts of cytokines (e.g., TNFα, IL-1β, and IL-6) are produced by activated microglia and astrocytes target cholinergic neurons. In addition, AGE is proinflamatory to activate microglia. Apoptotic or necrotic neuron death secreting ATP further activates microglia. Such a positive feedback loop of inflammation ensures AD pathogenesis [181]. There are elevated TNFα, IL-1β, and IL-6 in PD patients, which accompanies with caspase-3/8 activation consistent with neuronal apoptosis for the pathogenesis. Apart from elevated cytokines (e.g., IL-6 and TNFα), there are increased COX-2 expression and PGE2 level in PD patients. PGE2 diffuses into the brain parenchyma and activates catecholaminergic and serotonergic brainstem nuclei that innervate the paraventricular hypothalamus (PVH), bed nucleus of the stria terminalis (BNST), and central nucleus of the amygdala (CeA). IL1β activates the vagus nerve that in turn stimulates primary and secondary projection areas including the dorsal motor complex, PVH, BNST and CeA.

4.7.2 Common Pharmacologic Approaches

(a) γ-Secretase inhibitors prevent amyloid precursor protein (APP) cleavage into pathological Aβ42. (b) Anti-Aβ mAb decreases Aβ oligomer/aggregation. (c) Acetylcholine (Ach) facilitates neurotransmission, while (d) Ach esterase inhibitor (e.g., donepezil, galantamine, rivastigmine) brings up Ach level for neurotransmission. (e) L-DOPA supplies dopamine bioavailability. (f) Monoamine reuptake inhibitors maintain neurotransmitter level in synaptic cleft for continuous transmission. (g) Catechol-O-methyltransferase inhibitors (tolcapone and entacapone), and monoamine oxidase B inhibitors (rasagiline, selegiline) reduce dopamine metabolism to improve dopamine bioavailability. (h) Pramipexole and talipexole (D2-receptor agonists) inhibit the *in vitro* α-synuclein ag-

gregation and cytochrome C release or Lewy body formation, limiting DOPAL toxicity and neuron death. (i) Tetrabenazine, a specific inhibitor of vesicular monoamine transporter, decreases dopaminergic neurotransmission. (j) TREM-2 antibody activates TREM2 receptor; TREM-2 is responsible for Aβ42 internalization/trafficking and ApoE reception, preventing Aβ deposition and delaying Aβ pathology and neurofibrillary tangle formation. (k) Deep brain stimulation involves inhibiting cells and exciting fibers, changing firing rate of basal ganglia, electrical current acting on synapses to trigger neighboring astrocytes to release neurotransmitters (adenosine and glutamate), increasing cerebral blood flow, and stimulating neurogenesis.

4.7.3 Polyphenolic Actions

(a) Curcumin and EGCG phosphorylate CREBP that in turn activates BDNF that is required for long term potential and cognition process in hippocampus [31,32]. (b) Curcumin inactivates $\alpha/\beta/\gamma$ secretases that otherwise cleave APP into Aβ, thereby suppressing of AD progression along with intracellular neurofibrillary tangle formation [28–31,70]. (c) Resveratrol, curcumin, and quercetin directly inhibit monoamine oxidase that otherwise catabolizes neurotransmitters (e.g., 5-HT, epinephrine, DOPA, dopamine, *etc*.), therefore exhibiting antidepressive property and cognitive improvement [31,70]. (d) The ability to inactivate p38 MAPK (e.g., NF-κB inactivation, reduced glutamate excitotoxicity, and recovering synaptic plasticity, anti-apoptosis, *etc*.) (please refer to 3.3 (*27*)) by polyphenols in part contributes to neuroprotection in easing AD patholgy and Aβ toxicity [182]. (e) In the context of antioxidation (please refer to 4.1) in terms of both chemical structures and cellular functions, polyphenols could target the pathogenesis of neurodegeneration for full protection. (f) In view of anti-inflammatory effects by polyphenols, SirT1 activation (please refer to 3.2 (*8*)), NFκB inactivation (please refer to 3.2 (*11*)), NLRP3 inactivation (please refer to 3.2 (*20*)) (autophagy upregulation), TLR suppression (please refer to 3.4 (*40*)), and many others readily antagonize against CNS inflammation. (g) Resveratrol markedly reduces CSF, MMP9, IL-12p40, IL12p70, and RANTES while increasing macrophage-derived chemokine (IL-4), FGF-2, and plasma MMP10, showing induced adaptive immunity.

In summary, fighting against the pathophysiology (please refer to 4.7.1 (a) & (b) of neurodegeneration by polyphenols offer broad coverages compatible to current pharmacological approaches (please refer to 4.7.2 and Table 1) including AMPK-dependent & mTOR-inhibiting rapamycin, γ-secretase inhibitors, monoamine reuptake inhibitors, *etc*. Thus far, clinical trials have echoed protection of neurodegeneration by polyphenols [183–191].

4.8 Anti-Infections

Recent research has illustrated that polyphenols display antimicrobial potentials. The inhibitory mechanism(s), however, remain unclear. The mounting *in vitro* data, however, pave the way to clinical trials for their efficacies in human infections. (a) Resveratrol inhibits G (+) bacterial growth including *M. smegmatis, Bacillus cereus, Helicobacter pylori, Vibrio cholerae, Arcobacter cryaerophilus*, *Campylobacter coli, Mycobacterium tuberculosis, Neisseria gonorrhoeae*, *etc.*, which is greater than their effects on G (-) bacteria. In addition, it alters bacterial expression of virulence including reduced toxin production, inhibition of biofilm formation, reduced motility, and interference with quorum sensing. Interestingly, resveratrol binds reversibly to ATP synthase, partially inhibiting both ATP hydrolysis and ATP synthesis functions of the ATP synthase in the facultative aerobe (e.g., *E. coli*) [192], thus inhibiting oxidative phosphorylation. ATP hydrolysis also being inhibited in *Mycobacterium smegmatis* [192], and the metabolic activity of Arcobacter spp. being reduced [192]. (b) In fact, resveratrol displays better antifungal than antibacterial activity against *Candida albicans, Trichophyton mentagrophytes*, *Trichophyton tonsurans, Trichosporon beigelii*, *Trichophyton rubrum, Epidermophyton floccosum, Microsporum gypseum, Saccharomyces cerevisiae*, *etc*. (c) Apart from the anti-inflammatory effects on easing cytokine storm, polyphenols, especially green tea catechins (e.g., EC, ECG, EGC, and EGCG), show anti-viral activities *per se* against both DNA (HBV, HSV, EBV, *etc.*) and RNA (HCV, HIV, influenza, ZKV, EBOV, rota/entero-, *etc.*) viruses by inhibiting their entry, genetic replication, viral protein procession, *etc*. [193,194]. For instance, (*i*) inhibition of HBV RNA, DNA, and cccDNA synthesis and antigen expression contribute to antagonism against HBV. EGCG as an antagonist of the farnesoid X receptor alpha thus downregulates the transcriptional activities of the HBV. EGCG also targets replicative intermediates of DNA synthesis, interferes with transcription of the HBV core promoter, inhibits different genotypes of HBV entry into host cells, and reduces HBV replication by opposing HBV-induced incomplete autophagy. (*ii*) Flavonoids, EC, ECG, EGC, and EGCG show strong anti-HSV activity by destruction of the virion structure and inhibition of HSV-1 attachment by interacting with the virion surface. (*iii*) The anti-EBV lytic infection mechanisms of EGCG could be associated with inhibition of the MEK/ERK1/2 and PI3K/AkT signaling pathways (please refer to 3.3 (*22*), (*27*), *etc.*). (*iv*) The anti-HIV activities include inhibition of HIV reverse transcription, inhibition of viral entry into target cells by interfering with the interaction of receptors with the HIV envelope, inhibition of p24 antigen production, and EGCG strongly binding to CD4 D1 domain reducing the formation of the gp120/CD4 complex. (*v*) The anti-HCV activity is mainly mediated by inhibition of the HCV entry (e.g., impairment of viral attachment by altering viral particle structure), prevention of cell-to-cell transmission, suppression of HCV RNA replication, interference with HCV replication by downregulating COX-2 (please refer to 4.2 (*7*) & (*11*)), and targeting the HCV virion to prevent attachment to heparan sulfate. (*vi*) EGCG anti-influenza actions include as an influenza restriction factor, reduction of IAV and IBV by preventing viral adsorption to cell surface, inhibition on acidification of endosomes and lysosomes, and reduction of viral neuraminidase and RNA synthesis of viral genome. (*vii*) Polyphenols are even able to inhibit ACE2 receptor binding activity in SARA-CoV2 infection. (*viii*) The fact that autophagy suppresses viral infection independent of STING pathway could readily switch on polyphenolic potential in anti-viral defense in general (please refer to 3.2 (*20*) concerning AMPK activation/mTOR inhibition-dependent autophagy upregulation).

4.9 Miscellaneous

It is not surprising, the potentials of multi-targeting by polyphenols confer wide antagonisms against disease progression by either prevention or intervention measures. As a consequence of immunomodulation in addition to the classical anti-cancer activities, polyphenols also show anti-autoimmunity (e.g., diabetes I, RA, MS, psoriasis) and anti-allergy (e.g., food allergy, asthma, eczema). For instance, EGCG, curcumin, quercetin, apigenin, silibinin, and blackberry polyphenols inhibit bone marrow-derived DC maturation and expression of MHC molecules, reducing antigen uptake and decreasing secretion of the proinflammatory cytokines IL-1/2/6/12.

4.9.1 Promoting Longevity

In view of the ability to inhibit mitochondrial ATPase (please refer to 3.1 (*4*)) and activate AMPK (please refer to 3.2 (*7*)) and its downstream SirT1 (please refer to 3.2 (*8*)), polyphenols could be in line with calorie restriction for longevity. Moreover, the polyphenolic action on mTOR inhibition (please refer to 3.2 (*15*), 3.3 (*33*)) readily supports metabolic downregulation for anti-aging approach.

4.9.2 NAFLD protection

NAFLD is generally characterized with inflammation, insulin resistance, hepatic TG/VLDL-TG overload/accumulation (obesity), and oxidative stress. The anti-oxidative (please refer to 3.1 (*1*) to (*6*) & 4.1), anti-inflammatory (please refer to 4.2.3), anti-diabetic (please refer to 4.4.3), and hypolipidemic (anti-obesity; please refer to 4.5.3) capacities could certainly afford and make polyphenols beneficial to NAFLD that could progress to nonalcoholic steatohepatitis, liver fibrosis, or even hepatocellular carcinoma.

4.9.3 Easing IBD

IBD is a chronic inflammatory disorder caused by deregulated immune responses in a genetically predisposed individual. This is a complex process mediated by cytokines, chemokines, adhesion molecules, cytoplasm nuclear receptors, among others. IBD pathogenesis presents disrupted intestinal homeostasis, including gut microbiota population, barrier function, epithelial restitution, microbial defense, innate immune regulation (ROS generation, ER stress, autophagy, TLRs, NOD2, *etc.*), adaptive immunity (T/B imbalances), and cellular signaling. Genetic mutations also contribute to IBD pathogenesis. Genetic susceptibility, barrier defects, infection, sustained innate immunity, and their defective regulations/coordination in concert ensure the development of IBD. As a consequence of enhanced luminal bacterial invasion, the production of TNF-α and IL-1β/6/12/23 increases, triggering imbalanced T cells differentiation and further increased cytokine and chemokines for proinflammation. Consistent with the notion of elevated Th17 cells, IL-23 and its signaling on JAK-STAT activation mediate IBD. In these regards, it is plausible that IBD could share some genetic association with certain autoimmune disease.

Polyphenolic (quercetin, isoflavones, flavones, anthocyanins, *etc.*) benefits could readily extend to IBD that features gut inflammation and microbiota leakage. (a) The anti-inflammatory effects (e.g., NFκB inactivation, iNOS/COX2 downregulation, LOX-12 inhibition, suppressed cytokine TNFα, IL-1β/6/8, and IFNγ expression, upregulated IL-10, favored Th1/2 balance, *etc.*) [194–196] naturally contribute to anti-IBD. (b) Immunomodulation by polyphenols could ease IBD episodes as well as prevent its progression. Polyphenols reduce inflammation by suppressing the proinflammatory cytokines in IBD by inducing Treg cells in the intestine, inhibition of TNF-α, induction of apoptosis, and decreasing DNA damage. (c) As prebiotics and a consequence of altered microbiota with decreased species (*Bacteroides acidifaciens*) but increased species (*Ruminococcus gnavus* and *Akkermansia mucinphilia*), polyphenols induce Tregs while suppressing inflammatory Th1/Th17 cells, thereby preventing murine colitis development [196].

4.9.4 Anti-Anemia

The capabilities of polyphenols in anti-oxidation (please refer to 3.1 (*1*) to (*6*) & 4.1), antiinflammation (please refer to 4.2.3), and anti-infection (please refer to 4.8) are certainly responsible for fighting against iron deficiency anemia, a common form of anemia. Polyphenolic hypolipidemic actions in anti-obesity (please refer to 4.5.3) also lower the risk for such iron deficiency anemia.

Iron is the only micronutrient known to have a regulatory hormone (hepcidin) that responds to both nutrient status and infection [197]. Hepcidin, an antimicrobial peptide made in the liver, is a negative regulator of iron traf-

ficking; hepcidin binds iron exporter (ferroportin; FPN) to cause FPN internalization and degradation for consequent blocking not only iron release from cellular stores but also GI absorption of dietary iron [198,199]. Upregulated hepcidin dictates low plasma iron and its reduced bioavailability for heme/hemoglobin syntheses and effective erythropoiesis for red blood cell production, major characteristics of anemia. (a) ROS readily drives iron deficiency; sustained endogenous H_2O_2 induces hepcidin expression. Similar to IL-6 signaling (see below section on anemia of chronic inflammation), endogenous H_2O_2 mediates its positive action on upregulation of hepcidin expression by JAK1/STAT3 signaling pathway. Such activation mediated by H_2O_2 on hepcidin upregulation could provide mechanism by which infection or inflammation induces hepcidin expression. Interestingly, H_2O_2 shows synergistic positive effects on hepcidin expression with IL-6 and BMP6 [200]. (b) Inflammation upregulates hepcidin expression, resulting in so-called anemia of chronic inflammation. IL-6, IL-22, and type I IFN stimulate hepcidin transcription through STAT3 signaling [103]. Several microbial-derived TLR ligands can induce hepcidin expression, likely via induction of IL-6. SMAD and STAT3 signaling, which together also play a role in Th17 responses. (c) Infection also upregulates hepcidin expression [201]. Except HCV, infection or stimuli in general that invoke a systemic inflammatory response are likely to induce liver hepcidin expression, reduce serum iron, and increase iron accumulation in reticuloendothelial cells. (*i*) In bacterial infection, local neutrophils and MΦs also synthesize hepcidin in response to Gram-positive (group A Streptococcus) and Gram-negative (e.g., *Pseudomonas aeruginosa* or *Salmonella typhimurium*) bacteria in a TLR4-dependent fashion. Similarly in systemically, *P. aeruginosa* increases liver hepcidin mRNA levels. (*ii*) During parasitic infection, increased systemic hepcidin levels are observed during the blood stage of Plasmodium infection. Thus, lower serum iron levels and anemia are common in malaria. (*iii*) During viral infection, influenza A and *Candida albicans* increase liver hepcidin with concomitant reduction of transferrin saturation in animal models in which pathogens likely increase hepcidin via an inflammatory STAT3-mediated response [201].

4.9.5 Protection from Autoimmune APS

The antioxidative property (please refer to 3.1 (*1*) to (*6*) & 4.1) of polyphenols could protect against antiphospholipid syndrome (APS), a prothrombotic autoimmune disease being characterized by elevated auto-antibodies against phospholipid (cardiolipin), β2-glycoprotein I (β2 GPI), and/or prothrombin. Oxidative stress plays a key contributory role in APS pathogenicity of thrombosis, preeclampsia, and inflammation. (a) These antibodies activate neutrophil NOX and impair mitochondrial respiration, both of which promote ROS production [202]. (b) Oxidized β2GPI has a disulfide bridge between C32 and C60 within

domain I near B-cell epitope in the N-terminus, while another disulfide bridge is formed between C326 and C288 in the domain V near T-cell epitope in the C-terminus. The oxidized β2GPI immune complex causes EC damage/injury and activates protease disulfide isomerase; as a result, tissue factor is decrypted and activated, while FXI disulfide bridge is cleaved to become FXIa. Thus, APS manifests as thrombosis, inflammation, and preeclampsia [202,203]. The β2GPI immune complex also activates the classical pathway of complement, which leads to not only thrombosis but preeclampsia.

4.9.6 Relieving AMD

Age-related macular degeneration (AMD) is a multifactorial disease of the retina (e.g., changes in retinal vasculature), featuring degeneration and loss of photoreceptors and retinal pigment epithelium (RPE) cells. AMD pathogenesis includes oxidative stress for degeneration and death of retinal cells, which are mainly associated with aging, ROS overproduction, reduced antioxidants and antioxidant enzymes, and accumulation of damages to mitochondrial DNA. The macula concentrates light and displays high metabolic activity and high oxygen consumption associated with intense blood flow. In addition, inflammation in RPE, mutations in the complement factor H, epigenetic dysregulation, angiogenesis (e.g., upregulated TGFBR1, VEGF-A), HDL-C pathway (e.g., ApoE, CETP, and LIPC upregulation), immune dysregulation, *etc.* are also involved. Current treatments involve VEGF inhibitors and diet supplementation with vitamins C and E, zinc, copper lutein, n-3 FAs, and zeaxanthin.

Polyphenols with anti-oxidantive (please refer to 3.1 (*1*) to (*6*) & 4.1), anti-inflammatory (please refer to 4.2.3), anti-angiogenic (please refer to 3.3 (*23*)), and anti- aging/senescence (please refer to 3.2 (*8*) & (*15*), 3.3 (*33*)) activities contribute to AMD relief. (a) The anti-oxidative stress is mainly achieved by induced Nrf2 activation (please refer to 3.1 (*6*)), reduced A2E photooxidation, and suppressed mitochondrial dysfunction (please refer to 3.2 (*7*)). (b) The anti-inflammatory action in RPE cells is associated with downregulation of various IL signaling pathways, including IL-6/JAK2 (Janus kinase 2)/STAT3 (please refer to 3.3 (*28*)) as well as suppressed expressions of iNOS, COX2, TNF (please refer to 3.2 (*11*)), and complement factor B. (c) The ability to inhibit IP3K/AkT (please refer to 3.3 (*22*)) leads to BcL2 upregulation and Bax and caspase-3,9 inactivation for anti-apoptosis. (d) The upregulation on phagocytosis contributes to improve impaired cellular waste clearance, including AMD-specific deficient phagocytosis of the Aβ42 peptide and autophagy. (e) The anti-angiogenesis (please refer to 3.3(*22*) *PI3K/AkT/mTOR inhibition* and ref. [36]) is accomplished by suppressed EMT and VEGF.

4.9.7 Anti-Autoimmunity

In addition to *in vitro* cellular actions [204,205], clinical potentials of polyphenols (e.g., curcumin, resveratrol, EGCG, flavonoids, *etc.*) in treating autoimmune diseases (RA, psoriasis, MS, *etc.*) have recently been reported and reviewed [206–215]. (a) Concerning immunomodulation of Th17 downregulation, (*i*) EGCG reduces Th1 differentiation and numbers of Th17 and Th9 cells [204]. (*ii*) Grape seed pro-anthocyanidin extract exhibits anti-arthritic properties by upregulating the number of Tregs that contribute to the maintenance of immune tolerance and, therefore, the inhibition of autoimmunity [205] and by maintaining the balance between Th17/Treg for attenuating autoimmunity. Green tea polyphenol EGCG also induces Tregs, which similarly easing autoimmunity [207]. (*iii*) Rresveratrol decreases Th17 cell numbers; inhibited Th17 cell differentiation through the downregulation of phospho-STAT3/RORγt, whereas it promoted Treg differentiation by upregulating phospho-STAT5/Foxp3 [216]. Th17 readily marks autoimmunity [217]. (*iv*) Curcumin inhibits IL-17 production, easing autoimmune encephalomyelitis, epidermal hyperproliferation, abnormal keratinocyte differentiation, angiogenesis with blood vessel dilatation, and excess Th-1 and Th-17 cell infiltration, main histopathological features of psoriasis [218]. (b) In view of autoimmunity often leading to chronic inflammation, vice versa [102], diverse polyphenolic anti-inflammatory effects naturally ease autoimmunity. For instance, downregulation on TLR expression, NFκB, and proinflammatory cytokines (TNFα, IL-1β/6) by curcumin in part contributes to anti-inflammation and ease autoimmunity. By downregulating inflammatory cytokines such as IL-1β, IL-6, IL-12, TNF-α and IFN-γ and associated JAK-STAT, AP-1, and NF-κB signaling pathways in immune cells, curcumin inhibits autoimmune diseases [209]. (c) In conjunction with oxidative stress leading to autoimmunity (e.g., RA), the anti-oxidative stress (please refer to 3.1 (*1*) to (*6*) & 4.1) by polyphenols could ease RA [219].

4.9.8 Anti-Allergy

The immuomodulation by polyphenols has been reported as translational studies [220–225]. (a) In response to the immunomodulation (please refer to 3.4 (*46*)), for instance, shifting Th1/Th2 balance, (*i*) polyphenols (e.g., flavonoids, caffeic acid, *etc.*) could affect allergic sensitization and re-exposure to the allergen, which is largely mediated by binding to allergic protein, suppressed MHC II expression or co-stimulatory molecules (CD80, CD86), decreased Th2 cytokines, T inactivation, *etc.*; (*ii*) polyphenols could also regulate the Th1/Th2 balance and inhibit antigen-specific IgE antibody formation, showing asthma relieving; (*iii*) curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through JAK/STAT pathway; (*iv*) polyphenols also improve allergic contact hypersensitivity by regulating the balance of

Th1/Th2/Th17/Treg cell subsets; (*v*) by activation of Th1 and inhibition of Th2 and Th17 in a mouse model, gallic acid alleviates nasal inflammation of allergic rhinitis; and (*vi*) quercetin inhibits histamine production and proinflammatory mediators and regulates the Th1/Th2 stability/balance with the potential effect on allergic diseases. (b) Polyphenols increase the growth of probiotics: *Bifidobacterium* and *Lactobacillus*, known to have beneficial impacts in food allergies. (c) By targeting the pathogenesis of allergy [226–233], the effective polyphenolic anti-oxidative stress (please refer to 3.1 (*1*) *to* (*6*) & 4.1) readily eases allergic asthma, atopic dermatitis, and beyond.

5. Perspectives

The quarter-century explorations have demonstrated that polyphenols offer a broad spectrum of health benefits [5,44,108,156]. Table 1, if not exclusively, summarizes polyphenolic actions, which is somewhat compatible to common pharmacological approaches to inflammation, CVD, diabetes, obesity, cancer, neurodegeneration, and viral infection. Interestingly, polyphenols are multi-targeting and functional, nearly covering the most or combined drug actions in combating non-communicable metabolic symptoms and others as well as communicable viral infection; it certainly not only makes polyphenols suitable supplements for health prevention, but also advances them to therapeutic applications.

5.1 Era of Nutraceutics

Natural ingredients/products readily promote health and serve as a platform for drug developments. In addition to vitamins (A/B/C/D/E/F) are vital for life, naturally occurring bioactive substances such as aspirin, statins, rapamycin, metformin, paclitaxel, penicillin, *etc*. become active therapeutic applications for years.

5.1.1 Natural Ingredients Preventing Disease Progression

(a) Till now, phytochemical aspirin [234] remains mostly recommended for cardioprotection; the American Heart Association strongly advocates low dose NSAID aspirin (e.g., 80 mg) daily for healthy hearts. (*i*) Its classical COX1 inhibition arrests PGE2 and TxA2 production; PGE2 is proinflammatory, while TxA2 is responsible for vasoconstriction and platelet aggregation. (*ii*) Such common blood-thinner aspirin essentially activates AMPK and promotes resolvin (Rv) formation from n-3 PUFAs [108,123], which presents a wide range of antiinflammation. (*iii*) In transcellular metabolisms, COX-2 acetylation by aspirin undergoing conformational changes leads to 18R-HpEPA or 17R-HpDHA formation [235]. The R form derivatives are continually metabolized by 5-LOX and epoxide hydrolase in neutrophils; thus, RvE1 and at-RvD1 are formed from EPA and DHA, respectively. In a close relation to cardioprotection, RvE1 reduces ADP-stimulated platelet aggregation, TxA2 generation, P-selectin mobilization, and

actin polymerization in a calcium-independent manner; RvE1 counter-regulation of ADP activation is ChemR23-dependent [123]. (*iv*) Furthermore, acetylated COX-2 catalyzes AA conversion to 15(*R*)-HETE that then through 5-LOX reaction followed by hydrolysis results in epi-LXA4 and epi-LXB4 derivatives, two potent anti-inflammatory mediators. Beyond cardioprotection, aspirin, a "wonder drug", has also been used for diabetes, colorectal cancer, inflammation, Alzheimer's, and many other medical applications. (b) Ever since compactin or mevastatin being extracted from fungi by Endo group in 1976 [236], statin family compounds have been identified to competitively inhibit HMG-CoAR, a regulatory enzyme in the pathway, for effectively blocking cholesterol *de novo* biosynthesis in lowering blood cholesterol and offering cardioprotection. Beyond hypocholesterolemic action, statins also exhibit anti-oxidation (NOX inhibition, HO-1 activation, and Nrf2 activation), antiinflammation (CRP suppression [116], AMPK activation [113], eNOS activation, FOXO upregulation, IKK inhibition, NFκB inactivation, JAK/STAT inhibition [114,115], PI3K/AkT/mTOR inhibition, NLPR3 inactivation, increased IL-10, attenuated proinflammatory biomarkers, *etc*.), anti-thrombosis (platelet aggregation, tPA induction, downregulation of PAI-1 and TF expression, *etc*.), and anti-hypertension (decreased ET-1 expression, upregulated eNOS and NO bioavailability, and downregulated AT$_1$R expression). (c) Metformin (e.g., galegine or isoamylene guanidine) originating from herb Galega officinalis has been developed into anti-diabetes therapy, decreasing blood glucose inputs (hepatic gluconeogenesis and intestinal glucose absorption) and improving insulin sensitivity (increased peripheral glucose uptake and utilization). In addition, the ability to activate AMPK readily shows anti-oxidative stress and anti-inflammatory effects, being referred to as another "wonder drug" including cancer chemoprevention. (d) Terpenoid paclitaxel, also known as taxol from bark of pacific yew tree (*Taxus brevifolia*), is used for treating lung, ovarian, and breast cancer, as well as Kaposi sarcoma, gastroesophageal, endometrial, cervical, prostate, and head and neck cancers, in addition to sarcoma, lymphoma, and leukemia, killing tumors by mitotic arrest. In principle, paclitaxel stabilizes the microtubule polymer and protects it from disassembly; chromosomes are unable to achieve a metaphase spindle configuration, thus blocking the progression of mitosis and prolonging activation of the mitotic checkpoint for triggering apoptosis or reversion to the G0-phase of the cell cycle without cell division. The mitotic checkpoint delays separation of the chromosomes, which enter mitosis as replicated pairs of sister chromatids, until each pair has made stable attachments to both poles of the mitotic spindle. The presence of a small number of unattached kinetochores arrests cells in mitosis (e.g., metaphase and contain near-normal, bipolar spindles) by inhibiting the anaphase-promoting complex/cyclosome. Thus, such mitotic arrest results in either cell death during

mitosis or an abnormal exit from mitosis to form a tetraploid G1 cell without chromosome segregation or cytokinesis. In addition, it is proposed that taxol might directly cause cell death in interphase without having an affected earlier phase in the mitosis. (e) Potent immunosuppressive and anti-proliferative rapamycin disrupts cytokine signaling that promotes lymphocyte growth and differentiation. (*i*) Rapamycin impedes progression through the G1/S transition of the proliferation cycle, resulting in a mid-to-late G1 arrest. Initially, rapamycin binds to intracellular proteins (FKBP), thereby forming a unique effector molecular complex. The FKBP-rapamycin complex specifically targets mTOR, a Ser/Thr kinase on the upstream of (p70s6K) and cdk2-cyclin E. Thus, rapamycin leads to p70s6k inhibition or p27-induced cdk2-cyclin E inhibition, downregulating cell growth and proliferation by cell cycle arrest. (*ii*) Its inhibition on mTORC1 naturally suppresses purine/pyrimidine biosynthesis, reducing protein expression and cell proliferation. (*iii*) Its function in autophagy induction also exhibits anti-infections by decreased proliferation and growth for pathogen clearance and death. The clinical application of rapamycin includes inflammatory (e.g., obesity) and aging related pathological conditions such as cognition decline, Alzheimer's, cancer, and kidney, heart, and autoimmune diseases [34–39,237]. (f) Named after mould *Penicillium notatum*, penicillins, a family of broad spectrum β-lactam antibiotics, are effective against staphylococcal and pseudomonal bacterial infection by blocking peptidoglycan biosynthesis (transpeptidases inhibition) and glycosylation in membrane/cell wall synthesis.

5.1.2 Drug Platform

The well-known modes of actions could build polyphenols suitable candidates for therapeutic drug development. Concerning drug biochemical actions, (a) polyphenol-induced AMPK activation is analogous to antiinflammatory (e.g., aspirin, methotrexate, pemetrexed, acadesine, and salicylate) [238] and anti-diabetes (e.g., metformin, phenformin, and A769662) agents [239]. It is noted that AMPK activation is a key metabolic regulator for metabolic symptoms; (b) its direct and indirect mTORC1 inhibition could make polyphenols compatible to rapamycin benefits in clinical practices. Such mTORC1 inhibition could also lead to longevity benefits along with polyphenol-induced AMPK/SirT1 activation similar to caloric restriction; (c) polyphenol-mediated signaling enzyme/pathway inhibition such as IP3K/AkT/mTOR, PKC, MAPK/ERK, NFκB, *etc.* readily confer anti-proliferation and pro-apoptosis in anti-cancer strategies, neuroprotection, and beyond; and (d) in addition to powerful autophagic consequence of antioxidation and antiinflammation, autophagy upregulation *per se* by polyphenols could play a unique role in combating a host of diseases such as inflammation, cancer, neurodegeneration, infection, *etc.*

5.2 Future Directions

Further basic research as well as clinical trials warrant polyphenolics being healthy and combating disease development and progression. In-depth understanding the pharmaco- kinetics and dynamics including half-lives, pH resistance, lability, bioavailability, shelf-lives, metabolites, *etc.* of polyphenolics will advocate nutraceutical applications. Clinical trials could guarantee therapeutic benefits especially focusing on the bioavailability, dosage, effectiveness, and efficacy or toxicity, if any, of polyphenol intakes.

(a) Although vegetable and fruit consumption are healthy and highly recommended; a fundamental question remains: how much is effectively enough for health promotion concerning polyphenol bioavailability? Whether could such daily supplementation be transformed/extended or developed into drug formulation even for therapeutic applications? (b) Whether are polyphenolic candidates fulfilling potent antioxidation together with other multiple biological targets in improving human health? Thus far, vitamin C and E are well-established antioxidants; vitamin C coupled with glutathione system fights against biological oxidation in the aqueous phases, while vitamin E (α-tocopherol) scavenges free radicals in the lipid phases. It remains unclear whether there is any antioxidant as powerful as vitamin C & E. Will be polyphenols as effective as vitamin C/E in human health promotion? Will lipophilic polyphenols specifically ease membrane damage/oxidation for a broad spectrum of actions? (c) It remains largely elusive if polyphenols have any profound effects on endocrine system that plays a key role in cell signaling dictating health and diseases. For instance, thyroid hormone is critical for metabolic controls. Growth factor (e.g., EGF/VEGF) overexpression drives tumorigenesis. Insulin secretion could be relevant to many health statuses not only limiting to diabetes issues. (d) Several nuclear receptors (e.g., PPARα, FXR, LXRα, GR, CAR, PXR, *etc.*) are the targets of polyphenols or phytochemicals for exerting metabolic impacts on carbohydrate, lipid, or drug metabolisms. The clinical relevance remains largely unclear as to whether such affected nuclear receptors are fine-tune mechanism(s) for precise metabolic regulations along with diverse cell signaling regulations. (e) Immune system holds a crucial role in health maintenance. Although research has shaded lights on the complex issues in the beginning phases, it remains largely unclear whether polyphenols could consistently and widely boost immunity in accordance with different pathological settings. (f) Polyphenols are able to alter microbiota profiles/diversity [240,241]; however, it still remains its infancy in understanding the complex microbiota issues *per se* in human health and diseases. Microbiota diversity favors anti-obesity, anti-diabetes, anti-food allergy, antiinflammation, immune boosting, host energy harvesting, facilitating cancer immune checkpoint blockade efficacy, anti-autoimmunity, *etc.* Whether could altered microbiota

profiles consistently mediate polyphenolic beneficial actions? In a related consideration of gut microbiota contributing to drug/xenobiotic metabolism(s), whether could microbiota metabolize polyphenols? Whether could such metabolism(s)/metabolite(s) benefit or attenuate polyphenolic action(s)? (g) Antimicrobial potentials of polyphenols [242,243] have been reported primarily *in vitro* without clearly established mode(s) of actions, which could however pave the way to clinical trials for broadening their healthy applications. (h) The epigenetic (non-DNA mutation/chromatin modification) and miRNA (gene silencing/mRNA degradation/ translational blockade) effects also warrant further research. Food components (e.g., folic acid, vitamin B12, choline, zinc, selenium, *etc.*) are known to undergo epigenetic manipulations as well as RNA ribozyme modifications [244]. EGCG decreases the expression of oncogenic miRNAs (miR-92, miR-93, and miR-106b) and increases the expression of tumor-suppressor miRNAs (miR-7-1, miR-34a, and miR-99a) in human cancer cells, while curcumin up-regulates miR-22 and down-regulates miR-199a, showing improved cancer outcomes. The ability to undergo epigenetic modifications and miRNA genetic modulations [80–82] could be expected to substantially extend polyphenolic benefits in fighting diseases [245] beyond anti-cancer.

In summary, the research community (basic/translational research and clinical trials) as a whole welcomes innovative discoveries, looking forward to significant developments within the next quarter century for shaping up polyphenol as a main stream in therapeutic applications to improve/promote human health.

Abbreviations

ACC, acetyl-CoA carboxylase; ACE, angiotensin converting enzyme; Ach, acetylcholine; AF, atrial fibrillation; AGE, advanced glycation end-product; AkT, protein kinase B; AMD, age-related macular degeneration; AMPK, AMP-activated protein kinase; ANGPTL, angiopoietin-like; AP-1, activated protein-1; APC, activated protein C; Apo, apolipoprotein; APP, amyloid precursor protein; aPTT, activated partial thrombin time; AT III, antithrombin; AT, angiotensin; ATC, adoptive T cells; ATRA, all *trans* retinoic acid; AXL, receptor tyrosine kinase AXL (anexelekto; uncontrolled); BAS, bile acid sequestrants; C/REBP, cAMP response element-binding protein; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CM, chylomicron; COX, cyclooxygenase; CRP, C-reactive protein; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DPP-4, dipeptidyl peptidase 4; EC, endothelial cell; ECM, extracellular matrix; EGC, epigallocatechin; EGCG, EGC gallates; EPA, eicosapentaenoic acid; ERK, extracellular signal regulated kinase; ET, endothelin; FAS, fatty acid synthase; FBG, fibrinogen; FH, familial hypercholesterolemia; FIIa, thrombin; FOXO, Forkhead box O; GAS6, growth

arrest-specific 6 protein; GC, gallocatechin; GI, gastrointestine; GLP-1, glucogan-like protein-1; GP, glycoprotein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; GPx1, glutathione peroxidase 1; GSK3β, glycogen synthase kinase 3β; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis B virus; HDL, high density lipoprotein; HDL-C, HDL-cholesterol; HF, heart failure; HIF, hypoxia inducible factor; HIV, human immunodeficiency virus; HMGB1, high mobility group box 1; HO-1, heme oxygenase-1; HSL, hormone sensitive lipase; HSYA, hydroxysafflor yellow A; 5-hydroxy-dC, 5-hydroxydeoxycytidine; hyperTG, hypertriglyceridemia; IBD, inflammatory bowel disease; IDO, indoleamine 2,3-dioxygenasebe; Idol, inducible degrader of LDLR; IFN, interferon; IKK, inhibitor kappa B kinase; IL, interleukin; iNOS, inducible NOS; I/R, ischemia/reperfusion; IRS, insulin receptor substrate; IsoP, isoprostane; JAK, Janus kinase; JNK, Jun N-terminus kinase; LDL, low density lipoprotein; LDL-C, LDL-cholesterol; LDLR, LDL receptor; LMWH, low-molecular-weight heparin; Lp[a], lipoprotein [a]; LPL, lipoprotein lipase; LV, left ventricular ; LX, lipoxin; mAB, monoclonal antibody; MAPK, mitogen-activated protein kinase; MC4R, melanocortin 4 receptor; MCP-1, monocyte chemoattractant protein 1; MI, myocardial infarction; miR, microRNA; MMP, matrix metalloprotease; mTORC, mammalian/mechanistic target of rapamycin complex; MTP, microsomal triglyceride transfer protei; MΦ, macrophage; NAFLD, non-alcoholic fatty liver disease; NFAT, nuclear factor activated T; NFκB, nuclear factor kappa B; NLRP, NOD-like receptor protein; NOS, nitric oxide synthase; NOX, NADPH oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; NSAID, non-steroid anti-inflammatory drug; NT-proBNP, N-terminal pro–brain natriuretic peptide; OxLDL, oxidized LDL; PAF, platelet activating factor; PAI, plasminogen activator inhibitor; PAR, protease-activated receptor; PCSK, proprotein convertase subtilisin kexin; PDE, phosphate diesterase; PGC-1α, peroxisome proliferator-activated receptor coactivator; PGE2, prostaglandin E2; PGI2, prostacyclin; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator-activated receptor; PPO, polyphenol oxidase; PT, partial thrombin time; PTEN, Phosphatase and tensin homolog; RAAS, rennin-angiotensin-aldosterone-system; RCT, reverse cholesterol transport; ROS, reactive oxygen species; RPE, retinal pigment epithelium; Rv, resolvin; SCFA, short chain fatty acid; sGC, soluble guanylate cyclase; SirT, sirtuins; SOD, superoxide dismutase; SREBP, sterol response element binding protein; STAT, signal transducer and activator of transcription; SVEP1, sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1; TAFI, thrombin activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, TF pathway inhibitor; TG, triglyceride; TLR, Toll-like receptor; TMA, trimethylamine; tPA, tissue plasminogen activator; Treg, regulatory T cells; TSC, tuberous

sclerosis complex; TT, thrombin time; TxA2, thromboxane A2; UCP1, uncoupling protein 1; VLDL, very low density lipoprotein; VSMC, vascular smooth muscle cell; vWF, von Willebrand factor.

Author Contributions

AJC conceived the study, prepared the figures, wrote the manuscript, revised the manuscript, read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Not applicable.

Conflict of Interest

The author declares no conflict of interest. AJC is serving as one of the Editorial Board members of this journal. We declare that AJC had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MI.

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