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Polyphenols: A first evidence in the synergism and bioactivities

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ABSTRACT

Polyphenols are natural compounds and the most plentiful with synergistic properties contributing to potential health benefits. This review describes the synergistic interactions of polyphenolic compounds; as yet, no literature review has been undertaken to consider the experimental evidence of synergistic effects of polyphenols. The polyphenolic compounds claimed to have synergistic activities are highly effective against oxidation, peptic ulcers, myocardial infarction, tumors, and a variety of other conditions. In addition, anticancer activity via apoptosis and antibacterial, antifungal, anti-inflammatory, and estrogenic behaviors have also been reported. Apart from the synergistic effects of polyphenols, this review also illustrates their specific health benefits too and bioavailability in humans. The toxicity of some polyphenolic agents, including antinutritional effects, chronic nephrotoxicity, reduction in net protein utilization and antiluteinizing hormone, and tumor development, is also evaluated. Synergistic treatment approaches may be effective in the treatment of many diseases. These findings provide information about the benefits of polyphenol compounds in combination, which could be useful for future studies.

KEYWORDS

Synergistic effects; polyphenols; pharmacological activities; antioxidant; human health

Introduction

Polyphenols are naturally found in plant-based foods and have a variety of complex structures. The phenolic ring is the fundamental monomer in polyphenols, which are classified as phenolic acids and phenolic alcohols. According to the White–Bate–Smith–Swain–Haslam (WBSSH) definition, polyphenols are substances with a large enough number of dihydroxyphenyl and/or trihydroxyphenyl units that have multiple displays of these phenolic motifs in their monomeric forms, either due to their oligomeric nature or due to their oligomeric nature. It can meet the criterion as long as it is water soluble.[1] They are structurally diverse in nature and widespread in plants. In addition to this structural diversity, polyphenols in plant tissues are generally found as glycosides or complex polymerized substances with high molecular weights, such as tannins or in combination with many organic acids. There are various natural polyphenols, some of which are primarily used for dyeing fabric and tanning leather. Phenolic acids,

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flavonoids, tannins, stilbenes, and lignans are the main classes of polyphenols, and examples of polyphenolic compounds include gallic acid, caffeic acid, ferulic acid, kaempferol, quercetin, cyanidin, daidzein, and resveratrol.[1–4]

Polyphenols are an emerging area of interest for human health. Many studies have demonstrated the health benefits of polyphenols, which can play a crucial role in regulating metabolism, chronic diseases, weight, and cell proliferation. Plenty of polyphenolic compounds have been reported to date, but they have not been thoroughly characterized for their short- and long-term health effects. Animals, humans, and epidemiological experiments indicate that many polyphenols have antioxidant and anti-inflammatory properties that may preventively and/or therapeutically influence a range of non-communicable disorders, including cardiovascular and neurodegenerative diseases, cancer, and obesity.[5–8] For example, they can be protective against different neurodegenerative disorders, such as Parkinson's, Alzheimer's, and Huntington's disease.[8–11] Tang et al. found that a high rate of consumption of turmeric containing the polyphenol curcumin is suggested to contribute to the low incidence of Alzheimer's disease.[12] There are many population-based trials have shown that the reduced incidence of obesity correlated with dietary consumption of polyphenols may be confounded by the fact that foods high in polyphenols, being nutrient-dense, lead to a lower total intake of calories.[8,13–17] Furthermore, phenolic compounds also act as anti-inflammatory agents by maintaining the redox balance to alleviate oxidative stress and by reducing inflammatory responses by attenuation of cytokine pathways.[18] Additionally, flavonoids, including anthocyanins, flavones, catechins, flavanones, flavanols, and isoflavones, can neutralize free radicals and reduce the risk of cancer by preventing tumor cell development.[13]

According to Tallarida, sometimes two or more medications that individually provide apparently similar effects have considerably amplified effects when combined. If the combined effect is higher than its individual strengths suggest, the combination is said to be synergistic. A synergistic interaction allows lower dosage of combined components, which can reduce adverse effects.[19] In the treatment of various diseases, such as cancer, cardiovascular diseases, there are a variety of adverse effects. The synergistic action of two or more drugs can reduce the adverse effects in these therapeutic approaches. Generally, polyphenols are secondary metabolites generated by higher plants, which have a wide range of synergistic effects, principally as antioxidants, antidiabetic, anticancer, anti-inflammatory, antimicrobial and antihypertensive agents, in combination with other compounds. Although various polyphenols may be found in various plant sources, only a handful of them have synergistic effects. We have identified 15 most notable polyphenols of various experimental data which have potential synergistic effects.[20–33] Other polyphenols also have different therapeutic effects but they don't have significant synergistic effects. This review aims to bring together experimental evidence-based synergistic effects of polyphenols because no literature review to date has considered it. An additional aim of the review is to advance new research ideas for future studies.

Classification of polyphenols

In higher plants, several thousand compounds have a polyphenol structure and several hundreds of them are found in food plants. These molecules are secondary metabolites of plants and are mainly used for the protection against UV radiation or pathogenic aggression. These compounds can be categorized into distinct groups, depending on the number of phenol rings contained therein and the structural components that connect these rings. The major polyphenol groups include phenolic acids, flavonoids, tannins, stilbenes, and lignans; these groups are further categorized into many subclasses that are described below (Table 1).[1] In addition to this variety, polyphenols can be combined with and with different carbohydrates and organic acids.

The areas of application of natural polyphenolic compounds are extensive and provide both physiological and commercial benefits. For example, pomegranate peel, which is rich in tannins and other polyphenols, is used for dyeing non-synthetic fabrics in the Indian subcontinent.[34,35] Polyphenols, particularly tannins, have been used historically for leather tanning,[36] and are currently

Table 1. Classification and sources of polyphenolic compounds.

Polyphenols	Sub classes	Examples	Sources	References
Phenolic acids	Hydroxybenzoic acids	Protocatechuic acid, gallic acid	• Gallic acid: Black radish, red fruits, and onions • Protocatechulic acid: Food plants, including Hibiscus sabdariffa, *Olea europaea, Eucommia ulmoides, Vitis vinifera*, and *Citrus microcarpa* Bunge	[110,111]
	Hydroxycinnamic acids	Caffeic acid, coumaric acid, curcumin, ferulic acid,	Blueberry, coffee, coffee beans, pear, cranberry, lemon, cherry (sweet), apple juice, apple, orange, grapefruit, spinach, cherry juice, peach, potato, lettuce, tea, cider etc.	[112,113]
Flavonoids	Flavonols	Kaempferol, myricetin, quercetin	• Quercetin: spices, vegetables, fruits, beverages, fruit juices, soups • Myricetin: Vegetables, red wine, fruits, tea, berries, nuts • Kaempferol: grapes, apples, green tea, tomatoes, onions, potatoes, Brussels sprouts, broccoli, peaches, squash, lettuce, cucumbers, green beans, spinach, raspberries, blackberries	[114–120]
	Flavones	Luteolin, apigenin	• Luteolin: Celery, oregano, broccoli, parsley, green pepper, dandelion, thyme, perilla, carrots, chamomile tea, peppermint, olive oil, navel oranges, rosemary • Apigenin: parsley, chamomile, celery, vine-spinach, artichokes, and oregano	[114,120,121]
	Flavanones	Eriodictyol, hesperetin, naringenin	• Eriodictyol: Lemons and rosehips • Hesperetin: Bitter orange, orange, petit grain, lime, lemon, orange juice	[114,120,122]
	Anthocyanidins	Cyanidin, petunidin, malvidin delphinidin, pelargonidin	Tea, wines,, vegetables, fruits, olive oil, nuts, cereals, blueberries, cranberries, black currants, merlot grapes, red grapes, strawberries, raspberries, bilberries and cocoa	[120,123,124]
	Isoflavones	Genistein, daidzein	Soyabeans, other leguminous plants	[120,125]
Tannins	Condensed tannins	Polymers of polyhydroxyflavan-3-ol monomers	Grape seed, strawberries, apple juice, raspberries, walnuts, pomegranate, muscadine grape, blackberry, olive, peach, plum, black-eyed peas, chick pea, lentils, red/white wine, haricot bean, cocoa, tea, chocolate, cider, immature fruits and coffee	[113,126,127]
	Hydrolyzable tannins	Esters of gallic acid (gallo- and ellagi-tannins)		
Stilbenes	Phytoalexin	Resveratrol	Red wine, peanuts, grapes, peanut products, and soy	[128–130]
Lignans	Classical lignans and neolignans	Secoisolariciresinol, sesamol, enterodiol, pinoresinol, coniferyl alcohol	Flax seed, flaxseed, soybeans, sesame seed, cereals (wheat, rye, oat, and barley – rye being the richest source), cruciferous vegetables, including cabbage, and broccoli, and some fruits, particularly strawberries and apricots	[131–135]

applied in green chemistry as precursors for development of resins and plastics through polymerization processes for use in particleboard adhesives with[37] or without formaldehyde.[38,39] Chemical structures of the representative polyphenols are shown in Fig. 1.

Synergistic effects of polyphenolic compounds

Polyphenols are some of the most widely available plant secondary metabolites from dietary sources. Although phenolic compounds are not considered essential micronutrients, many studies have shown their positive influences on human health, particularly with regard to dietary conditions associated with high fruit and vegetable consumption. In higher plants there are several compounds which have a polyphenol structure and several hundred are present in food plants. However, only 15 of these provided experimental proof in the case of synergistic effects, that's why we concentrated on 15 polyphenols in our review. In addition, they have been observed both in vivo and in vitro to perform

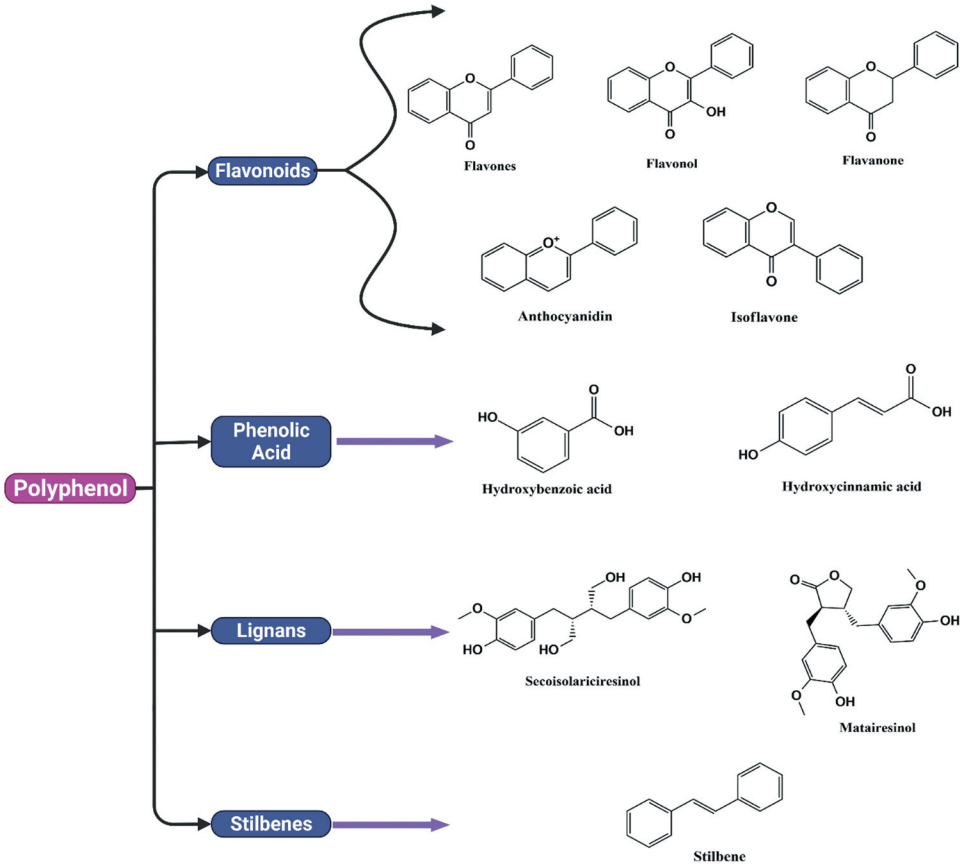

Figure 1. Classification of polyphenols.

anti-inflammatory, anticancer, antidiabetic and antioxidant activities in combination with other active compounds (Table 2). The mechanisms of action of synergistic effect of different polyphenols in the different therapeutic effects are illustrated in Fig. 2.

Curcumin

Turmeric (*Curcuma longa*), a spice that belongs to the ginger family has received a great deal of attention, mostly from scientific/medical, and dietary perspectives. Many studies have shown that curcumin targets numerous signaling molecules and cellular activity, contributing to its beneficial attributes. Favorable effects of curcumin have been established for metabolic disorders, inflammatory conditions, pain, and degenerative eye conditions. In addition to these benefits, curcumin ameliorates nephritic disorders and oxidative damage.[20] However, many studies have reported that curcumin causes synergistic effects to a significant extent. Sreenivasan et al. tested the synergistic effects of curcumin and anticancer agents on human retinoblastoma cancer cell lines. Curcumin triggered a concentration-dependent reduction in cell proliferation and cell kinetics and even induced apoptosis in the retinoblastoma cell lines. When curcumin was paired with anticancer medications, such as etoposide, carboplatin, and vincristine, for administration to the human retinoblastoma cells lines, cell cycles and cell viability were substantially decreased and caspase 3 activities was enhanced compared to the individual effect of the compounds. In both retinoblastoma cell lines, the likely mechanism

Table 2. Synergistic effects of polyphenolic compounds.

Synergistic interactions	Doses (mg)/ concentrations (μM/ %)	Subjects	Assay	Activity	References
Alpha-tocopherol + Ferulic acid	5 μM + 5 μM	n. m.	Fluorescent probe BODIPY	Highest antioxidant action	[39]
Ascorbic acid + Tocopherol	0.02% + 0.2%	Fish oil	AOCS official method	Antioxidant action	[40]
Curcumin + DDMN	2–10 μM + 3–15 μM	Human	MTT assay	Inhibition of cell growth of HCT116 colon cancer cells	[41]
Curcumin + Piperine	2.5–100 μM + 2.5–50 μM	SH-SY5Y cells	MTT and ThT assay	Neuroprotective action	[42]
Curcumin + Insulin	40 μM + 0.1 μM	Mice	MTT assay	Glucose metabolism	[43]
Curcumin + Epigallocatechin	50 μM + 100 μM	Human	Western blot analysis, flow cytometric analysis	Antiproliferative action in PC3 prostate cancer cells	[44]
Curcumin + Vincristine Curcumin + Carboplatin Curcumin + Etoposide	10 μM + 0.050 μM 5 μM + 20 μg 5 μM + 0.1 μg	Human	MTT assay	Reduction in cancer cell proliferation and cell kinetics, and also apoptosis induction	[21]
Luteolin + Celecoxib	50 μM + 75 μM	Human	TUNEL assay, XTT assay, trypan blue exclusion method, Western blot analysis	Breast cancer cells apoptosis, Cell viability	[45]
Luteolin + Quercetin Luteolin + Imipenem	800 μg + 400 μg n. m.	MRSA isolates	MIC assay	Anti-MRSA action	[46]
Luteolin + Sulforaphane	12.5 μM+6.25 μM 25 μM+1.25 μM	Raw 264.7 macrophages	ELISA assay	Anti-inflammatory action	[26]
Gallic acid + Rosmarinic acid Gallic acid + Caffeic acid Gallic acid + Chlorogenic acid Gallic acid + Quercetin Gallic acid + Rutin	150 mg+150 mg 150 mg + 600 mg 150 mg + 600 mg 150 mg + 150 mg 150 mg + 150 mg	n. m.	FRAP assay	Anti-oxidant action	[47]
Gallic acid + Famotidine	100 mg + 10 mg 50 mg + 10 mg	Wistar rats	ANOVA test	Antiulcer action	[48]
Gallic acid + Curcumin	50 μM + 30 μM	Human	MTT assay	Anticancer action	[49]
Caffeic acid + Paclitaxel	20 mg/kg + 10 mg/kg	Human	Western blot analysis	Antitumor and anticancer effect by increasing apoptosis of H1299 cells	[50]
CAPE + Caspofungin	16 μg/ml + 0.125 μg/ml	n. m.	Checkerboard assay	Disruption of iron homeostasis, antifungal action	[27]
Ellagic acid + Ferulic acid	1:1 ratio	n. m.	DPPH assay	Antioxidant action	[51]
Ferulic acid + Ascorbic acid	20 mg/kg + 80 mg/kg body weight/day	Rats	LSD test	Cardioprotective action	[52]
Kaempferol + Fluoroquinolones	n. m.	n. m.	MIC assay	Anti-MRSA action	[53]
Kaempferol + 5-fluorouracil	2:1, 1:1, 1:2 and 4:1	n. m.	Western blot analysis	Inhibition of colorectal cancer cells growth	[29]
Quercetin + Catechin	3 μM + 75 μM	Murine macrophage RAW 264.7 cells	Western blot analysis, MTT assay, ELISA assay	Anti-inflammatory action	[54]

(*Continued*)

Table 2. (Continued).

Synergistic interactions	Doses (mg)/ concentrations (μM/ %)	Subjects	Assay	Activity	References
Quercetin + Sulfamethoxazole	100 mg/mL + 15 mg/ mL	Mice	MIC Assay	Antibacterial activity	[55]
Myricetin + Phenolic acid derivatives (caffeic acid, para-coumaric acid, vanillic acid)	n. m.	BALB/c mice	HPLC-PDA method	Against dengue fever-related thrombocytopenia	[56]
Myricetin + α-tocopherol	100 ppm + 250 ppm, 200 ppm + 125 ppm, 200 ppm + 250 ppm	n. m.	Gas chromatography	Antioxidant action	[57]
Myricetin + Sulforaphane	100 μM + 40 μM	Mice	MTT assay, ELISA assay	Induced apoptosis in 3T3-L1 adipocytes and reduced cell viability	[58]
Myricetin + Piceatannol	200 μM + 100 μM	Human	MTT assay, Western blot analysis, TUNEL assay	Anticancer action	[59]
Cyanidin + Acarbose	1 μM + 0.05 μM 1 μM + 3.12 μM	n. m.	n. m.	Intestinal maltase inhibition Intestinal sucrase inhibition	[33]
Baicalein + Daidzein	0.1 μM + 0.5 μM 1 μM + 5 μM	Human	MTT assay	Induce estrogenic behavior	[22]
Morin + Rutin	800 μg/ml + 800 μg/ ml	n. m.	Antibiotic sensitivity assay, MIC Assay	Anti-MRSA action	[23]
Resveratrol + Cisplatin	2.5 μM + 20 μM	Human	Hoechst staining, flow cytometry and Western blot analysis	Induce apoptosis via modulating autophagic cell death in A549 cells.	[25]
Resveratrol + Curcumin	10 mg/kg + 200 mg/ kg	Male Albino rats	Lipid peroxidation and antioxidant assays	Against fipronil-triggered oxidative damage	[24]
Apigenin + Paclitaxel	n. m.	HeLa cells	TUNEL assay, Western blot analysis	Cancer cell apoptosis	[60]
Genistein + Tamoxifen	1–40 μM + 1–40 μM	n. m.	Flow cytometric analysis	Work on the hepatocellular carcinoma cell line	[61]

n. m.: Not mentioned; **MTT**: 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide; **FRAP**: Ferric Reducing Antioxidant Power; **ELISA**: Enzyme-linked immunosorbent; **MRSA**: Methicillin-resistant *Staphylococcus aureus*; **MIC**: Minimum inhibitory concentrations; **ThT**: Thioflavin T; **DDMN**: 3′,4′-didemethylnobiletin; **AOCS**: American Oil Chemists' Society; **CAPE**: Caffeic acid phenethyl ester; **DPPH**: 2,2-diphenyl-1-picryl-hydrazyl-hydrate; **LSD**: Least significant difference.

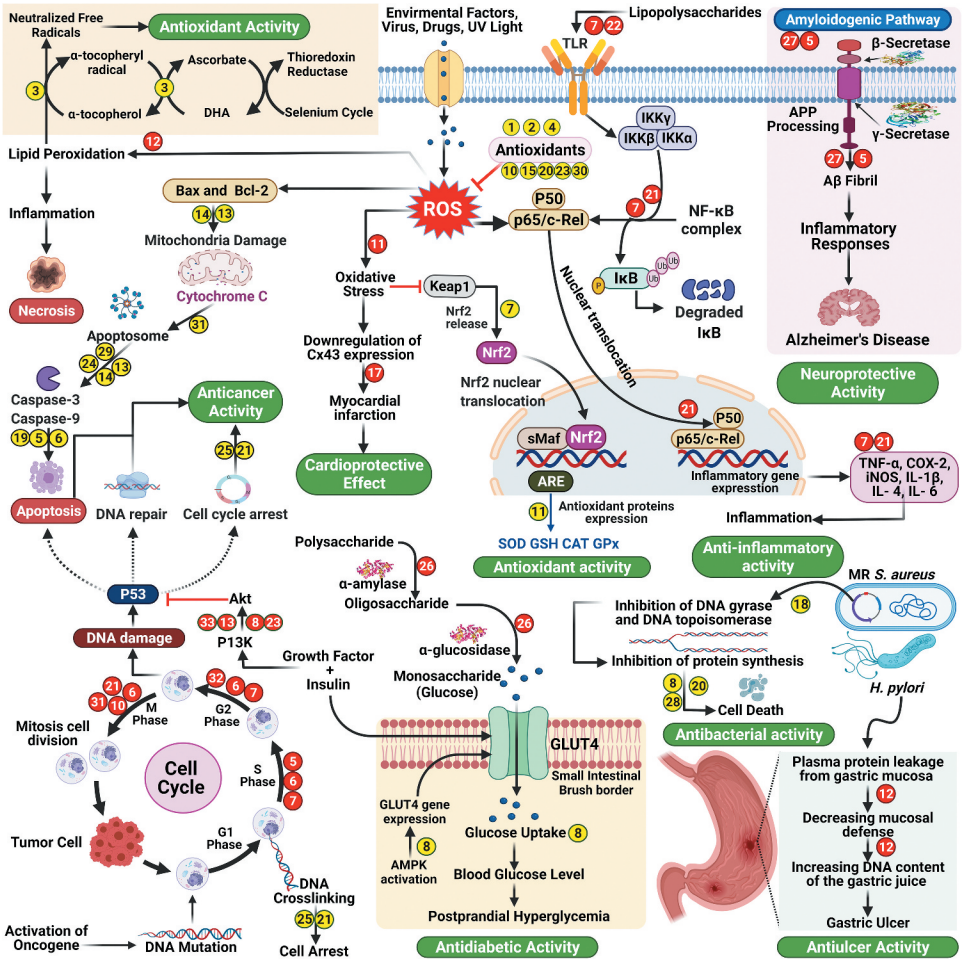

Figure 2. Mechanism of synergistic effects of polyphenols. Here the numbers highlighted with yellow color represent stimulation and red color represent inhibition. The numbers indicate following synergism. 1. Curcumin and Etoposide/Carboplatin/Vincristine synergism. 2. Curcumin and Sulfinosine synergism. 3. Curcumin and Epigallocatechin Gallate synergism. 4. Curcumin and Insulin synergism. 5. Curcumin and Piperine synergism. 6. Curcumin and 3′,4′-didemethylnobiletin synergism. 7. Luteolin and Sulforaphane synergism. 8. Luteolin and Quercetin synergism. 9. Luteolin and Celecoxib synergism. 10. Gallic Acid and Caffeic Acid synergism. 11. Gallic Acid and Protocatechuic Acid synergism. 12. Gallic Acid and Famotidine synergism. 13. Gallic Acid and Curcumin synergism. 14. Caffeic Acid and Paclitaxel synergism. 15. Ellagic Acid and Lipoic Acid synergism. 16. Ellagic Acid and Ferulic Acid synergism. 17. Ferulic Acid and Ascorbic Acid synergism. 18. Kaempferol and Fluoroquinolones synergism. 19. Kaempferol and 5-Fluorouracil synergism. 20. Quercetin and Sulfamethoxazole synergism. 21. Quercetin and Kaempferol synergism. 22. Quercetin and Catechin synergism. 23. Myricetin and α-Tocopherol synergism. 24. Myricetin and Sulforaphane synergism. 25. Myricetin and Piceatannol synergism. 26. Cyanidin-3-Galactoside and Acarbose synergism. 27. Baicalein and Daidzein synergism. 28. Morin, Rutin and Cephradine/Imipenem/Ceftriaxone/Methicillin synergism. 29. Resveratrol and Cisplatin synergism. 30. Resveratrol and Curcumin synergism. 31. Apigenin and Paclitaxel synergism. 32. Genistein and Tamoxifen synergism.

implicated in the combination of curcumin and chemotherapeutic drugs triggered cell-cycle arrest in the S-phase. According to Andjelkovic et al., a combination of curcumin and sulfinosine therapy at concentrations used 7.5 μM and 1 μM respectively caused a more significant cell-cycle arrest in the S and G2/M phases in NCI-H4660/R cells.[62] Besides, the same activities were shown in HOS cells with the higher concentration of 10 μM when curcumin was used along.[63] In RB cells, Sreenivasan et al. also noticed a significant elevation in caspase 3 expression in combination treatment compared to single drug treatment. Their findings are comparable to those of LevAri39 & Hosseinzadeh et al., who found that treating osteoarthritis synovial adherent and cardio myoblast cells with a combination of

curcumin and celecoxib caused synergistic pro-apoptotic effects.[64] Therefore, Sreenivasan et al. (2015) concluded that curcumin–single anticancer drug combinations show remarkable synergistic inhibitory activity, and recommended curcumin as a therapeutically potent modulator against retinoblastoma cancer.[21] Curcumin has also been demonstrated to enhance the cellular accumulation of chemotherapeutic medicines such as doxorubicin on cancer cells by boosting their effects. According to Hosseinzadeh et al., Curcumin in combination with doxorubicin has a synergistic effect in H9c2 cardio myoblast cells.[64] Likewise, the combination of curcumin with paclitaxel increases paclitaxel's anti-cancer actions on Hela Cells through a mechanism that controls the activation of NF-kB and the Akt pathways.[65] A research investigated the combined effects of curcumin and epigallocatechin gallate on PC3 prostate cancer cells and established potential synergistic action against these cancer cells. Epigallocatechin gallate was administered to PC3 cancer cells at concentrations of 50 μM and 100 μM in the presence of 50 μM of curcumin. Epigallocatechin gallate inhibited proliferation of PC3 cells by 11.2% and 24.3% at 50 μM and 100 μM, respectively, whereas with curcumin, the effect rose to 34.8% at the 50 μM concentration. By co-treating Epigallocatechin gallate and curcumin, the p21 protein expressions were greatly raised, while the treatment with each individual chemical was not changed. In addition, this combination therapy has arrested both S and G2/M phases on PC3 cells. These findings demonstrate the increased inhibitory impact of Epigallocatechin gallate on PC3 cell proliferation by curcumin through the synergistic up-regulation of the growth stoppage induced by p21 and further cell growth arrest.[44] Kang et al. found a synergistic relationship between insulin and curcumin, with both acting on glucose metabolism in muscle cells. Curcumin treatment strongly mediated glucose uptake and phosphorylation of AMP-activated protein kinase, but not phosphoinositide 3-kinase/Akt. Interestingly, the insulin and curcumin co-treatment resulted in reciprocal synergism by activating both AMPK/ACC and PI3-kinase/Akt pathways. However, no synergism was detected with insulin and epigallocatechin gallate co-treatment. The outcomes of this study highlight that curcumin, as a prospective antidiabetic agent, facilitates AMP-activated protein kinase activation and glucose absorption with improved insulin sensitivity at concentrations used 40 μM and 0.1 μM, respectively in muscle cells.[43] In addition to these research reports, many synergistic effects of curcumin have also been established against neural disorders, colon cancer cells, breast cancer cells, and bacteria-induced infectious diarrhea. Using in silico and in vitro assays, Manap et al. demonstrated synergism between curcumin and piperine in strongly inhibiting amyloidogenesis and acetylcholinesterase as well as showing a substantial neuroprotective effect in SH-SY5Y cells when both are used at concentrations ranging from 2.5–100 μM.[42] But when curcumin used along, they produce same effect on neuroblastoma cell line (SH-SY5Y cells) at the concentration of 20 μM.[66] In addition, a recent report by DiMarco-Crook et al. showed for the first time synergism between curcumin and 3′,4′-didemethylnobiletin against colon cancer HCT116 cell growth. The combined action resulted in substantial G2–M cell-cycle blockage as well as extensive apoptosis, which significantly outdid the effects of treatment only with curcumin or 3′,4′-didemethylnobiletin.[41]

Luteolin

Luteolin, a polyphenolic compound in the flavone group of flavonoids, is well documented for its many biological activities, such as pro-oxidant, antiallergic, estrogenic and antiestrogenic, anti-inflammatory, anticancer, and antiapoptotic activity.[67] Luteolin's pharmacological activities may be associated with each other. In addition, the anticancer characteristics of luteolin are related to the induction of apoptosis and suppression of cell growth as well as angiogenesis and metastasis. Luteolin is also regarded as a potent antioxidant compound, which works by destroying free radicals, especially reactive oxygen species (ROS) .[68] It is well recognized for its synergistic actions which may confer physiological benefits. In an in vitro experiment of luteolin in combination with sulforaphane, Rakariyatham et al. observed strong anti-inflammatory activity and determined combinational impacts of luteolin and sulforaphane on inflammatory obstruction in RAW 264.7 macrophages caused by lipopolysaccharides. Sulforaphane and luteolin together demonstrated dose-dependent suppression

of lipopolysaccharide-induced nitric oxide formation in different combination 25 μM+1.25 μM and 12.5 μM+6.25 μM. Their combined action resulted in stronger inhibition of nitric oxide production compared to the action of single compounds for example luteolin along produce same result at the concentration of 20 μM.[69] They act synergistically as anti-inflammatory agents by reducing pro-inflammatory protein expression, including by stimulation of STAT3, NF-κB pathway, etc., through which inflammatory proteins, especially COX-2, iNOS, IL-1β, and IL-6, can be regulated. In addition, sulforaphane and luteolin reduced cellular ROS as well as improved the expression of cellular antioxidant proteins, such as HO-1 and Nrf2.[26] According to Amin et al., both quercetin and luteolin in combination with a number of antibiotics inhibited the MRSA bacterium. In addition, luteolin demonstrated efficacy against clinical isolates as well as the MRSA ATCC 43300 strain; these effects increased considerably in conjunction with quercetin, and the combination of quercetin and luteolin with antibiotics had additive effects against MRSA. The FICI findings, in particular, suggested additive and synergistic relationships between these flavonoids and antibiotics.[46] Other studies have also established synergistic effects of luteolin. One study tested the combinational apoptotic action of luteolin and celecoxib against breast cancer cells, and found the luteolin–celecoxib mixture to strongly inhibit cellular growth at the concentration of 50 μM + 75 μM. The combination therapy considerably reduced the viability of cancer cells, and was more effective in killing tumor cells in comparison to the treatment with agent alone. The combination therapy showed a larger rise in apoptosis of the breast cancer cell. After luteolin and celecoxib combination treatment, lower levels of akt phosphorylation (pAkt) were also observed.[45]

Gallic acid

Rancidity and oxidation of oils and fats can be prevented by gallic acid and its derivatives, including lauryl gallate, octyl gallate, propyl gallate, hexadecyl gallate, and tetradecyl gallate; this ability is ascribed to their antioxidation properties and free radical scavenging. They may be promising as additives in food industries.[70] A range of studies on the biological and pharmacological activities of these phytochemicals has focused on the antioxidative, anti-inflammatory, antimicrobial, anticancer, gastroprotective, cardioprotective, and neuroprotective activities of gallic acid in the diet and its ester derivatives as flavorings and preservatives. Many studies have also measured the synergistic activity of gallic acid combined with various active compounds for therapeutic purposes. Hajimehdipoor et al. tested the synergistic antioxidative activity of some phenolic and flavonoid compounds, including gallic acid, caffeic acid, quercetin, rosmarinic acid, and chlorogenic acid. A mixture of 150 μM of gallic acid and 600 μM of caffeic acid demonstrated more potent synergistic antioxidant activity (137.8%) than the individual compounds.[47] According to Hugo et al., the gallic acid and protocatechuic acid combination show considerable synergistic action against oxidation.[71] A study investigated the synergistic effect of gallic acid–famotidine mixture at different doses in rats and found promising antiulcer activity compared to their individual effects. The protection from these combinations can be attributed to their anti-secretory and antioxidant activity, as demonstrated by a decrease in gastric juice, free acidity ulcer index, pH, and total acidity. Their combinations have also reduced the leaking of the plasma protein which improves the mucosal barrier. Increased mucosal defense is also demonstrated by a decline in cell exfoliation as the lowering of the gastric juice DNA content is detected.[72] The lowered level of DNA in all drug groups further indicates the rise in the gallic acid, famotidine and their compounds' mucosal defensive ability. Moreover, their combinations therapy raises the concentrations of catalase, superoxide dismutase, reducing glutathione, lipid peroxidase, mylo peroxidase and the dehydrogenase of glucose-6-phosphate in the tissue of stomach.[48] Some studies have shown that gallic acid in combination with curcumin has anticancer activity. According to Moghtaderi et al., gallic acid–curcumin mixtures at certain doses induce cytotoxicity and apoptosis in the human breast cancer cells MDA-MB-231. The analyzes of gene expression revealed that their combination down-regulated the expression of the anti-apoptotic protein Bcl-2 gene and up-regulated the expression of the pro-apoptotic protein Bax and caspase 3 genes. This shows that Gallic acid along with Curcumin

has increased apoptosis of MDA-MB-231 cells at the concentration of 50 μM and 30 μM. The same result also demonstrates by Chen et al., that the combination cause apoptosis in cancer cells by PARP cleavage and caspase-3 activation.[73,74] According to these results, it can be concluded the combination of Gallic acid and Curcumin causes the activation of caspase 3 and PARP cleavage, which can significantly enhance apoptotic cells than the medication alone.[49] But when gallic acid used along, they produce efficacious apoptosis and DNA damage was observed at 50 − 500 μM.

Caffeic acid

Caffeic acid is a polyphenol formed via secondary metabolism of plants, and is found in olives, fruits, coffee beans, carrots, potatoes, propolis, etc., and is the major hydroxycinnamic acid available in human diets. It is involved in plant defense against predators, parasites, and pathogens since it has a negative influence on the development of fungi, insects, and bacteria and facilitates the protection of plant leaves against ultraviolet B radiation.[75] In vitro and in vivo experiments have shown multiple physiological benefits of caffeic acid and its derivatives, including antibacterial, antiviral, antioxidant, anti-inflammatory, anti-atherosclerotic, antidiabetic, antiproliferative, liver defense, and anticancer activity. Its possesses the antioxidant and pro-oxidant efficiency, owing to its chemical composition with free phenolic hydroxyls, the number and location of OH on the catechol group, and the double bonds of the carbon chain.[75–79] Numerous studies have assessed the promising synergistic effects of caffeic acid and its derivatives. For example, research investigated the synergistic anticancer activity of a caffeic acid–paclitaxel mixture at different concentrations and found satisfactory activity against lung cancer by increasing apoptosis of H1299 cells. Tumor volume was decreased by 55% following intraperitoneal administration of 20 mg/kg of caffeic acid for three weeks. However, the combined use of caffeic acid and paclitaxel at 20 mg/kg and 10 mg/kg, respectively, reduced tumor volume by 80%.[50] A study investigated the synergistic effect of caffeic acid phenethyl ester (CAPE) with caspofungin (CAS) against *Candida albicans*; synergistic action was mediated by the disruption of iron homeostasis which results in fungal cell death.[27] CAPE-induced iron deficiency contributes to the downregulation of iron-utilization genes and upregulation of iron uptake. Taken together, the findings mean that CAPE's disturbance of iron homeostasis may underlie its synergism with CAS. The formation of cell wall components requires energy, most of it being supplied by the mitochondrial chain through oxidative phosphorylation. Therefore, CAPE-induced mitochondrial defects are related to increased susceptibility to CAS, possibly due to minimal ATP, which results in cell death.[27]

Ferulic acid

Ferulic acid is an omnipresent compound in plants synthesized during tyrosine and phenylalanine metabolism. It appears in leaves and seeds both in free form and covalently bound to lignin and other biopolymers. It has extensive therapeutic activity against cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders. Owing to its high antioxidant function, a wide range of activities beneficial to human health have been proposed for this phenolic agent. It is also a strong membrane antioxidant considered to have a protective effect on human health. It is an efficient free radical scavenger and is licensed in several countries as a food additive to prevent cell membrane peroxidation.[80–82] When ferulic acid attaches to a free radical, it transfers the hydrogen atom of the phenolic group to the radical and generates a stable phenoxy radical. This stable radical is incapable of initiating a new free radical chain reaction. Consequently, ferulic acid protects the cell membrane ferulic acid from peroxidation. Several in vivo and in vitro studies have analyzed the synergistic activities of this phenolic acid. Priyanka et al. established synergistic antioxidant effects of ferulic, lipoic, and ellagic acid. High antioxidant activity in methanol and aqueous ferulic acid solution (97% and 70%) was recorded for all three acids.[51] A methanol solution of ellagic acid and lipoic acid

(1:1) showed the highest antioxidant activity of the different mixtures, while ellagic and ferulic acid (1:1) had the highest aqueous solution antioxidant activity. The 1:1:1 mixture of all three acids showed the best antioxidant activity – 98% and 64% in methanolic and aqueous solutions, respectively. An in vivo analysis evaluated the cardioprotective role of ferulic acid and ascorbic acid in rats during isoproterenol-induced myocardial infarction. Application of isoproterenol for two days (150 mg/kg/body weight daily) contributed to a significant rise in lipid peroxidation, serum marker, and a large reduction in endogenous antioxidants in rats. However, oral application of a ferulic acid (20 mg/kg body weight/day)–ascorbic acid (80 mg/kg body weight/day) combination for six days considerably reduced these effects. This protection mechanism seems to be attributable to its antioxidant characteristics, as demonstrated by the improvement of antioxidant enzyme activity and the decrease in the amount of the oxidative marker MDA. Generally, Ascorbic acid is a good free radical scavenger, it may have shielded nitric oxide from being inactivated by free radicals, increasing its availability and so improving cardiac performance during myocardial ischemia. Ferulic acid, on the other hand, is renowned for protecting the cardiac antioxidant activity by reducing lipid peroxidation. As a result, the combination of them can help maintain the physiological integrity of free radical exposed cells. In addition, Metias et al. proposed that the density and positioning of the membrane Cx43 should be protected, as the Gap junction protein disruption could be a possible underlying cause for cardiac arrhythmias. According to immunohistochemistry, Cx43 expression was reduced and Cx43 was lost from areas of intercalated discs in cardiac tissues collected from the isoproterenol-induced myocardial infarction. Ferulic acid or Ascorbic acid administration enhanced Cx43 expression and retention in intercalated disc areas, while the combination of the two increased Cx43 presence to a higher extent at the concentration of 20 mg/kg and 80 mg/kg body weight/day. Further research is needed to determine whether the anti-oxidant characteristics of Ferulic acid and Ascorbic acid are the key underlying mechanism in this improvement or whether there is another alternative pathway that can describe it.[83]

Kaempferol

Kaempferol, present in fruits and vegetables, is an antioxidant. Several studies have identified the health benefits of dietary kaempferol, including reduced risk of chronic diseases, particularly cancer. It increases the body's antioxidant defenses against free radicals that induce cancer. Kaempferol has been documented at the molecular level to reduce a variety of major elements in cellular signal transduction pathways related to apoptosis, inflammation, angiogenesis, and metastasis. It has a substantial preventive effect on cancer cell proliferation and angiogenesis and causes apoptosis of cancer cells. On the other hand, it tends to retain the viability of normal cells, with a defensive impact in some cases[84] A number of epidemiological studies have described synergistic interactions of kaempferol with other active compounds. Prakash et al. showed synergistic activity of kaempferol and fluoroquinolones on MRSA. They proposed a probable synergistic mechanism for kaempferol derivatives, such as kaempferol-3-O-α-L-(2,4-di-E-p-coumaroyl)-rhamnoside (C2), kaempferol-3-O-α-L-(2-E-p-coumaroyl-4-Z-p-coumaroyl)-rhamnoside (C3), and quinolones. DNA gyrase and/or DNA topoisomerase IV may be the primary site of action of C2 and C3. DNA gyrase and DNA topoisomerase IV in bacteria are also the main targets of quinolones. Kaempferol derivatives and quinolones exhibit anti-MRSA properties by acting synergistically.[30] Another in vitro study analyzed the synergistic activity of kaempferol with 5-fluorouracil on the growth of colorectal cancer cells (CRC) by regulating the PI3K/Akt signaling pathway. Kaempferol with 5-fluorouracil had a synergistic anticancer impact by inducing apoptosis and modifying the levels of expression of thymidylate synthase in CRC cells.[29]

Quercetin

Quercetin is one of the significant bioflavonoids found widespread in fruits and vegetables and is known for its anti-inflammatory, vasodilator, anti-hypercholesterolemic, antihypertensive, anti-obesity, and anti-atherosclerotic behaviors. It is also reported to show antimicrobial properties, especially against almost all strains of bacteria affecting the gastrointestinal, urinary, respiratory, and dermal systems.[85–87] Its potential to be anti-infective and anti-replicative may lead to antiviral functionalities. Adenovirus, Japanese encephalitis virus, herpes simplex virus, and the respiratory syncytial virus usually react to flavonoids. Free radicals are one of the most significant causes of diseases, including vascular and metabolic disorders and hypertension.[85,88,89] Many studies have evaluated the synergistic effect of quercetin with other compounds. According to Heba et al., quercetin in combination with sulfamethoxazole showed potent antibacterial action during in vivo and in vitro analysis. When compared to individual use, the in vivo data demonstrated that their combination exhibited considerable improvements in liver and kidney functioning at the concentration of 100 mg/mL and 15 mg/mL. In addition, malondialdehyde level has decreased dramatically while catalase and superoxide dismutase activity have increased greatly in comparison to other treated groups. The spleen recovery was seen when *S. aureus* colonies disappeared compared to the infected one. Finally, in effective therapy of *S. aureus* infection with the sulfamethoxazole and quercetin combination reduced side effects of sulfamethoxazole while enhancing antibacterial efficacy, indicating that this combination could be used therapeutically in humans.[55] Jaramillo et al. experimentally analyzed synergistic antiproliferative action of quercetin and kaempferol in cultured human cancer cell lines and proposed that the combined use of the two compounds is more effective for decreasing cell proliferation than their individual application. The underpinning mechanism indicated quercetin's improved chemopreventive activity when combined with kaempferol by arresting HCT-116 cells in the G2/M cell cycle phase and inhibiting DNA synthesis, resulting in cell viability loss. These results imply that the combination of quercetin and kaempferol was able to successfully target the cellular machinery required for cell proliferation in this human colon cancer line which was growth hormone-independent.[90] Another study revealed the same result conducted by Imran et al. also mentioned that combining quercetin and kaempferol reduces cell proliferation more effectively than alone in the Caco-2 and HuTu-80 human intestinal cell lines as well as the PMC42 breast cancer cell line.[91] The exact mechanism by which this combination causes cytotoxicity in human colon cancer cells is unknown. In addition, combinational anti-inflammatory characteristics of quercetin and catechin were recently investigated by Li et al. They determined the synergistic influences of quercetin and catechin on inflammatory obstruction caused by lipopolysaccharides in RAW 264.7 macrophages on the concentration of 3 μM and 75 μM but the same effects have been produced by 100 mg/ml of quercetin along. The results show that catechin and quercetin together reduce lipopolysaccharide-induced pro-inflammatory agents, such as tumor necrosis factor α, nitric oxide, nitric oxide synthase, interleukin-1β, and cyclooxygenase-2, as well as blocking the stimulation of TLR4–MyD88-induced NF-κB and mitogen-stimulated protein kinase signaling pathway.[54]

Myricetin

Myricetin is a natural flavonoid obtained from plants and is well known for its importance in different food products. It is the main component of several drinks and foods. In addition, this compound possesses a wide range of biological activities such as potent anticancer, antioxidant, anti-inflammatory, and antidiabetic action. It also possesses many functions against diseases associated with the central nervous system, and a number of studies have reported that myricetin has potential as a defense against Alzheimer's disease and Parkinson's disease. Myricetin is used as a preservative to prolong the shelf life of foodstuffs containing fats and oils due to its capacity to safeguard lipids from oxidation.[92] Myricetin has also been found to show a considerable number of synergistic interactions with other active compounds. According to Anjum et al., myricetin acts synergistically with phenolic

acid derivatives against dengue fever-related thrombocytopenia in BALB/c mice. The findings of this study show that a polyphenol-rich portion of CPLJ may reverse acute thrombocytopenia by facilitating platelet recovery from megakaryocytes, thereby providing a strong rationale for its use in the management of thrombocytopenia associated with dengue fever.[56] In addition, a study conducted an in vitro study to assess the combined antioxidant influence of myricetin and α-tocopherol. They observed individual and synergistic interactions of myricetin and α-tocopherol at a variety of concentrations and reported that myricetin showed more potent antioxidant activity against autoxidation of omega-3 oil triacylglycerol compared to α-tocopherol in single assays. However, in the case of combined application, all mixture concentrations demonstrated synergistic activity, and the highest activity was shown by the total mixed concentration of less than 10 × 10–4 M.[93] An investigation by Yao et al. found that myricetin acts synergistically with sulforaphane to facilitate apoptosis in 3T3-L1 adipocytes. The mixture of myricetin and sulforaphane synergistically diminished cell viability, significantly reduced anti-apoptotic B-cell lymphoma 2 developments, and triggered apoptosis, at the concentration of 100 μM and 40 μM compared to the individual effects of the two compounds. This study also showed that stimulation of the mitochondrial apoptotic pathways regulated by threonine kinase 1 was facilitated due to myricetin/sulforaphane-induced apoptosis.[58] Moreover, myricetin shows selectively apoptotic activity with piceatannol in human cancer cells at the concentration of 200 μM and 100 μM but myrecetin produce same effect at higher than 100 μM.[94] Morales et al. discovered that piceatannol or myricetin-induced apoptosis occurs via a pathway of ROS-independent cell death. Piceatannol and myricetin have thereby triggered apoptosis synergistically in HL-60 cells, but not in HepG2 cell line. These data imply that dietary polyphenols' putative anti-carcinogenic activities are very dependent on the cell line employed. Human epidemiological investigations are needed to confirm the applicability of these findings.[59]

Cyanidin

Cyanidin and its glycosides commonly occur in human diets through the daily consumption of grains, fruits, vegetables, and red wine. The antidiabetic effects of cyanidin and its derivatives have been extensively studied. The combination of cyanidin-3-galactoside and acarbose is proposed to exert a synergistic influence on intestinal α-glucosidase inhibition.[33,95] Sarinya, Piyawan, and Sirichai's study on inhibitory activities of cyanidin and its glycosides and synergistic effects with acarbose against intestinal α-glucosidase and pancreatic α-amylase demonstrated that cyanidin and its glycosides (1 μM) were unable to exert an inhibitory influence on intestinal sucrose and maltase. However, acarbose showed considerable inhibitory action against intestinal sucrose and maltase. Therefore, intestinal maltase inhibition was improved when cyanidin-3-galactoside, cyanidin-3-glucoside, and cyanidin-3,5-diglucoside were applied in combination with acarbose (0.05 μM). In addition, pancreatic alpha-amylase inhibitory activity was not established for cyanidin and its glycosides (1.0 μM), but the cyanidin–acarbose combination showed strong activity against pancreatic alpha-amylase by increasing the inhibition rate.[33]

Baicalein

Baicalein and daidzein are flavonoid compounds belonging to isoflavone subclasses. They act as effectors activating the estrogen-mediated pathway and prevent Aβ-induced neuronal death. Neuroprotective properties of baicalein have been demonstrated against glutamate/NMDA activation, Aβ-induced toxicity, oxidative stress, glucose deprivation, and inflammation-mediated degeneration.[96,97] On the other hand, Daidzein is a phytoestrogen that is mostly obtained from soybean extracts and is used in clinical settings. According to indicators of estrogen neuroprotection, daidzein can develop memory and perform a neuroprotective effect in the brain.[98,99] The findings of Choi et al.'s investigation of the synergistic action of baicalein and daidzein in estrogenic and neuroprotective effects suggest that the estrogenic effect of flavonoids may be promoted by boosting

the working concentration 0.1 μM and 0.5 μM. However, baicalein (5 μg/mL) along can create the same neuroprotective effect.[100] Non-estrogen receptor-mediated signaling pathway or variable binding selectivity for estrogen receptor subtypes of baicalein and daidzein may elucidate the synergistic estrogenic effects of this combination. Daidzein can also amplify the effects of baicalein, resulting in the alteration of the solubility, absorption, distribution, metabolism and elimination of the other via several pathways for its neuroprotection or pharmacokinetic interaction with one flavonoid. However, because of drug solubility limitations and cytotoxicity, this might not be relevant in all situations. To overcome this challenge, combinations of different flavonoids with identical biological properties may be used to improve their cellular potency and to mitigate potential side effects of drugs when used at high concentrations. Based on this rationale, baicalein and daidzein were mixed at concentrations of 0.1 μM + 0.5 μM and 1 μM + 5 μM and investigated for their combined role in inducing estrogenic behavior. The analysis indicated that luciferase activity may be further improved under co-treatment concentrations relative to a single drug application.[22]

Morin

Morin, a natural bioflavonoid, is an essential component of traditional medicinal preparations. It was originally extracted from plants in the Moraceae family and is a component of several types of fruits and herbs, and wine. In vivo and in vitro analyses suggest that it may have anti-inflammatory, antioxidant, and antiproliferative effects, and it is widely present in food as well as in traditional herbal medicines. *Psidium guajava* (Indian guava) is also known to produce morin. Being an active compound in guava, morin is expected to demonstrate desirable attributes .[101,102] Amin et al. analyzed antibiotic synergistic and additive action of morin, rutin, and quercetin against MRSA. Their screening studies with antibiotics and flavonoids demonstrated flavonoid action against bacterial samples. The inhibitory areas were enhanced by combining the tested flavonoids with resistant antibiotics. When combined, the minimum inhibitory concentrations (MICs) of antibiotics and flavonoids were reduced. The combination of morin, rutin, and quercetin proved most efficient with MICs of 280, 280, and 140 μg/ml. Morin, quercetin, and rutin showed synergy with amoxicillin, cephradine, ampicillin, imipenem, ceftriaxone, and methicillin, while additive effects were detected for morin + rutin with cephradine, imipenem, ceftriaxone, or methicillin. However, morin and rutin alone did not show activity, but effects against bacterial samples were reported in combined treatment.[23]

Resveratrol (3,4,5-trihydroxystilbene)

Resveratrol is a phytoalexin present in several spermatophytes, including peanuts and Polygonum cuspidatum, an herb used in Chinese medicine. It is reported to have many beneficial attributes, including antitumor, antiviral, and vascular protective effects. The synergistic effect of the resveratrol–cisplatin combination on apoptosis via modification of autophagy in A549 cells was investigated by Hu et al. The anticancer activity of resveratrol relies on its elevation of apoptosis by promoting autophagy at the concentration of 500 mg/kg.[103] Resveratrol enhances the effect of cisplatin on apoptosis in A549 cells when the combination of resveratrol (2.5 μM) and cisplatin (20 μM) is used. According to their findings, cisplatin raised Bax protein levels while decreasing Bcl2 protein levels. Moreover, resveratrol could enhance the effects of cisplatin in A549 cells through altering the Bax/Bcl2 ratio. Furthermore, the development of autophagosomes and alterations in LC3-II and P62 levels revealed that resveratrol in association with cisplatin induced autophagy. In A549 cells, suppressing autophagy with 3-methyladenine significantly reduced the apoptosis induced by the combination of resveratrol and cisplatin. Flow cytometry and Hoechst staining further supported this, indicating that the combination therapy might cause apoptosis in A549 cells synergistically .[25] In addition, resveratrol has been established as an antioxidant agent. Through an in vivo analysis of the synergistic antioxidant effect of resveratrol with curcumin against fipronil-induced oxidative damage in male albino rats, AlBasher et al. established a potent effect when doses of 10 mg/kg of resveratrol and 200 mg/kg of

curcumin were applied. However, 0.5 mM of resveratrol produce same antioxidant activity when used along.[104] They found that combining Resveratrol and Curcumin alleviated and corrected fipronil-induced tissue oxidative stress, most likely through enhancing antioxidant defenses through their free radical scavenging activity and antioxidant properties. As the level of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione (GSH) were reduced, while nitric oxide (NO) and malondialdehyde (MDA) levels were considerably elevated in the renal, hepatic and brain tissues after fipronil administration. Finally, the enzyme levels were restored to normal after using a combination of Resveratrol and curcumin therapy.[24]

Apigenin

Apigenin is a dietary flavonoid compound with several health benefits. Biological activities have been shown for a variety of concentrations of apigenin, e.g., 25 mg/kg of apigenin strongly induced lysis in TC-1 tumor cells and substantially delayed tumor development. In addition to antitumor effects, apigenin possesses antidiabetic properties due to its ability to suppress α-glucosidase action, boost insulin secretion, and associate with and reduce cellular reactive oxygen species, by which diabetic symptoms can be prevented.[105] Some studies have described synergistic effects of apigenin with other compounds. A research investigated the effects of the combination of apigenin and paclitaxel on cancer cell apoptosis. Previous studies had shown the potency of both apigenin and paclitaxel in inducing cell apoptosis, and Xu et al. verified this effect in HeLa cells. Based on the findings of this study, the combined action is reported to be considerably better than the action of the single compounds. In addition, the TUNEL-positive cell staining rates improved notably from 17.95% and 19.65% in the paclitaxel- and apigenin-treated groups, respectively, to almost 40% in the combination-treated groups. Increased cytotoxic activity against cancer cells was also reported by Yimiao Xu et al. According to their findings, superoxide level was increased in HeLa cells treated with apigenin and paclitaxel combination or apigenin alone. So, the amount of ROS in HeLa cells was linked to apoptosis induced by apigenin and paclitaxel combination. Apigenin suppressed SOD enzyme activity but did not affect SOD protein levels, implying that apigenin promotes ROS buildup by lowering SOD enzyme activity. Simultaneously, findings from caspase-2 overexpression and knockdown experiments showed that caspase-2 was involved in apigenin and paclitaxel-induced death in HeLa cells. To evaluate the exact mechanism, they finally concluded that apigenin could sensitize cancer cells to paclitaxel-induced apoptosis by reducing SOD activity, which resulted in an increase of ROS and caspase-2 cleavage, implying that combining apigenin and paclitaxel was an efficient strategy to reduce the amount of paclitaxel used.[60]

Genistein

Genistein is a natural product that has been investigated extensively and shown to have a broad range of biological activities, such as antioxidant, anticancer, and antimicrobial properties. Genistein may bind to both α and β estrogen receptors, but it has a greater preference for the latter and is believed to perform its estrogenic activities via estradiol-like mechanisms.[106] A few studies have shown synergistic interactions between genistein and some metallic compounds, in which the combinational effect protects against ovariectomy-mediated bone loss.[107,108] In Chen et al.'s in vivo investigation, simultaneous ingestion of silicon and genistein resulted in protection against bone loss through upregulation of the ratio of OPG to RANKL. They assessed the mechanisms for bone protection of concurrent genistein and silicone intake by OPG/RANKL axis in ovariectomized rats. Their finding demonstrated that genistein and silicon therapy boosted the ovariectomized rats' bone mineral density (BMD). RT-PCR has shown that the administration of genistein and silicon can raise the expression of OPG mRNA significantly and reduce RANKL mRNA expression. Further Immunohistochemical staining findings demonstrated that the expression of OPG protein can enhance efficiently by genistein and silicone supplementation and decrease RANKL protein expression in bone tissue. This is the primary mechanism throughout ovariectomized rats is genistein and silicon.[108] Sanaei et al. proposed that genistein together with tamoxifen

work on the human hepatocellular carcinoma cell line at the concentration range of 1–40 μM for both. In case of genistein, 40 mg/kg along produce same anticancer effect.[109] In the HCC HepG 2 cell line, they found that genistein, tamoxifen, and their combination reduce proliferation and induce apoptosis. Genistein can cause apoptosis in HCC by a variety of mechanisms, including activation of numerous ER stress-related regulators such as m-calpain, caspase-12, GADD153 and GRP78. In addition, induction of caspase-3 in Genistein -treated HCC has been described, which promotes apoptosis and suppresses cell proliferation. They suppress NF-κB and Akt signaling pathways activation in breast and prostate cancers, which are both important for the balance between apoptosis and cell viability.[61]

Conclusion and future directions

Polyphenols are a group of natural bioactive compounds found in plants. They constitute a significant number of chemical compounds effective for treating diseases. The most important characteristic of polyphenolic compounds is their synergistic activity which makes them distinct from other natural bioactive compounds. The gallic acid and caffeic acid combination show potent synergistic antioxidant action (137.8%) at a concentration of 150 μM and 600 μM, respectively. The antiulcer activity has been reported for the gallic acid–famotidine combination. In addition, simultaneous use of caffeic acid and paclitaxel has shown high potency in reducing tumor volume. Although phenolic compounds play a significant role in providing therapeutic benefits, the exact mechanism of synergistic action is not established. Therefore, future research should focus on determining the mechanistic pathways of these bioactive compounds and how they confer health benefits synergistically. Although epidemiological studies of some polyphenols have been carried out to evaluate synergistic effects, in vivo analyses of some of these compounds have yet to be performed. Therefore, it is recommended that in vivo tests are performed for all phenolic compounds. Moreover, further studies should be undertaken to establish additional health benefits of these active compounds.

Authors Contributions

Saikat Mitra: Conceptualization, Formal analysis, Investigation, Writing - Original draft, Abu Montakim Tareq: Conceptualization, Formal analysis, Editing, Visualization, Rajib Das: Formal analysis, Resources, Editing, Talha Bin Emran: Resources, Conceptualization, Formal analysis, Writing – Review & Editing, Visualization, Supervision, Project administration, Firzan Nainu: Formal analysis, Writing - Review & Editing, Arka Jyoti Chakraborty: Formal analysis, Investigation, Islamudin Ahmad: Investigation, Discussions, Trina E. Tallei: Formal analysis, Writing – Review & Editing, Abubakr M. Idris: Formal analysis, Writing – Review & Editing, Jesus Simal-Gandara: Resources, Conceptualization, Formal analysis, Writing - Review & Editing, Visualization, Supervision.

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