Herbal phenolic acids: A review on their antioxidant effects, biochemical Properties and their clinical and experimental effects

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Received (xxx), Accepted (xxx)

Abstract

The earth has openhandedly offered a huge number of different herbs like ribwort, thyme, rosemary, basil, sage, cardamom, chamomile, and mint, which are rich in different types of polyphenols with potent biochemical and antioxidant characteristics. This paper concentrates on many natural phenolic acids and their common natural herbal origins. A summary of recent reports of antioxidant effects of phenolics in emulsions (o/w) is delivered as a lipid-based in the vitro-model system. Additionally, exploring the activities of phenolic acids could serve to elucidate their possible health effects toward oxidative conditions. Lastly, this review depends on the newest literature evidence that concerns specific biochemical characteristics of the studied phenolic acids.

Keywords: Herbal phenolic acids; Emulsion; Antioxidant agents; Health characteristics.

الخلاصة

تعتبر الأرض غنية جدا بالعديد من الأعشاب المختلفة مثل لسان الحمل والزعتر وإكليل الجبل والريحان والمريمية والهيل والبابونج والنعناع ، وهي غنية بأنواع مختلفة من مادة البوليفينول ذات الخصائص البيوكيميائية القوية ومضادات الأكسدة. يركز هذا البحث على العديد من الأحماض الفينولية الطبيعية ومصادرها العشبية الطبيعية المشتركة. كما يتم تقديم ملخص للتقارير الحديثة عن تأثيرات مضادات الأكسدة للفينولات في المستحلبات (o / w) كنظام قائم على الدهون في النظام المختبري التجريبي. بالإضافة إلى ذلك ، يمكن أن يساعد استكشاف أنشطة الأحماض الفينولية في توضيح آثارها الصحية المحتملة تجاه حالات الأكسدة. أخيرًا ، تعتمد هذه المراجعة على أحدث أدلة البحوث التي تتعلق بخصائص كيميائية حيوية معينة للأحماض الفينولية المدروسة.

الكلمات المفتاحية: الأحماض الفينولية العشبية. مستحلب؛ عوامل مضادة للأكسدة؛ الخصائص الصحية.

1. Introduction and aim of the review

By "herbal phenolics", several substances (e.g., phenolic acids, flavonoids anthocyanins, etc.) with different features in their structures that modify their antioxidant effects and the consequent effects on our health were stated [1,2]. Epidemiologically, some evidence stated that a diet with different plant foods significantly diminishes the hazard of many kinds of cancers and cardiovascular disorders, proposing that certain antioxidative agents found in the plant foods could be efficient for preventing cancer incidences and mortalities [3,4]. Polyphenolic compounds that originate in these cures are the main compounds responsible for biological activities and disease treatment [5]. Particularly, phenolic acids offer a noteworthy group of potent natural compounds, which have hydrophilic and hydrophobic properties that may prevent oxidative damage when used as active constituents in different systems of emulsion [6]. Researches in this field have concentrated on phenolic acids capacity for scavenging the reactive oxygen species (ROS) free radical (FR) and more specifically on slaking the FR, using the kinetic parameter as a measuring tool [7]. Over the past ten years, the food industries have considered the usage of natural phenolic compounds as an effective approach to inhibit oxidative damage in different foods and thus keep their important properties [8,9].

In different emulsified foodstuffs (e.g., sauces, bandages, desserts, and soups), the oxidation of lipids may happen easily because of the large surface area of these lipids [10,11] by different mechanisms (enzymatic and nonenzymatic oxidation mechanisms) [6], which are complicated, in comparison with bulk oils, and not completely clarified [12,13]. Moreover, the antioxidant effects in an interface may be vital to develop novel food products and explore the health effects of these compounds toward oxidative damage [14]. The different systems of emulsion usually imitate the important structural characteristics and amphiphilic nature of vital biological membranes that are exposed to oxidative damage during singlet oxygen attack and FR [15]. A distinctive instance of bio-emulsion is presented by different lipoproteins of blood plasma, which make the lipids available for the hydrophilic part of the body [16]. The start of these injurious biochemical mechanisms result in oxidative harm of various molecules, eventually can lead to the development of dangerous health conditions (i.e. cardiovascular diseases, carcinogenesis, and aging [17,18]. In the following sections, the review will show how these oxidative reactions prevented using different herbal phenolic compounds.

The review studies in the 2nd section the natural phenolic acids, which are extracted from different herbal sources, including eatable and other well-known plants. Then, a summary of the existing new study findings of antioxidant activities of various phenolic acid in systems of o/w emulsion was afforded, which also involved in vitro studies about the antioxidant efficiencies of phenolic acids in different types of emulsions that offer valuable background information and knowledge of nutritious attention, which act as a support to the clinical researches. Different clinical researches have concentrated on the possible activities of different phenolic acids toward the progression of cardiovascular and cancerous diseases, and different health conditions (e.g. bacterial infections, inflammations, and skin disorders, etc). The major goal of this paper is to offer in 3rd part a summary of the newest evident literature about the health valuable properties of the studied phenolic acids.

2. Natural origins of phenolic acid with their effects against oxidation of nutriment emulsion

This part of the review offers an overview of the most essential natural origins for some common phenolic acids of natural origins, which are scheduled in Table 1 together with chemical structures. In addition to that, different literature studies on the antioxidant activities for the tested phenolic acid versus the oxidative deterioration of o/w emulsion systems were achieved.

2.1 Caffeic acid

Caffeic acid is a type of hydroxycinnamic acid (HCA), its structure consists of phenolic and acryloyl group, which has trans derivatives, It is found in all plants because it is an intermediate in the biosynthesis of lignin, one of the major components of woody plant and its residues [19,20]. Some herbs have a high level of caffeic acid, particularly yerba mate and thyme with 1.5 gm/kg and 1.7 mg/kg of caffeic acid respectively [21,22]. In some fruits (e.g. pears, apples, and berries) caffeic acid was found in high quantities in p-coumaric acid (70–100%) of all HCA [23]. Additionally, caffeic acid was found in the Eucalyptus globulus bark [24] and was recognized as the chief phenolic acid in coffee [25]. Moreover, Cephalaria species was analyzed by Goren, *et al.* in 2019 using liquid chromatography with mass spectrometry and determined caffeic acid as a main phenolic acid [26].

Some researchers have described a strong antioxidant activity of caffeic acid in Tween-dependent emulsion (TBE) that is composed using vegetable oils like linoleic acid [7], flax seeds, sunflower as well as corn oil [27]. In (2017) Villeneuve *et al.* reported that caffeic acid acts as a prooxidant with a low level or absence of endogenous E-vitamers (tocopherols), while it showed a clear effect against oxidation in Tween-and Citrem-stabilized emulsions in presence of E-vitamers. Furthermore, they proposed that the detected difference in antioxidant activity in various emulsifiers and in the presence or absence of E-vitamers were caused due antioxidant–antioxidant as well as antioxidants-emulsifier interactions in the emulsion [28]. Present studies have clearly shown that caffeic acid was an effective antioxidant in different in vitro antioxidant assays.

2.2 Gallic acid

Gallic Acid is a type of hydroxylated benzoic acid, which is the major phenolic acid found in *Camellia sinensis* (tea plant) [29], in addition, is present in chestnut and some berries in high amounts [22]. Gallic acid is also found in many land plants (e.g. Maltese mushroom), aquatic plants (e.g. Eurasian watermilfoil), and the green-blue algae (e.g. *Macrocystis aeruginous*) [30,31]. Newly, Santos *et al*. have separated 0.8 mg/kg of gallic acid from the extract of black tea [32].

There are several contradictory shreds of evidence in this review concerning the efficiency of gallic acid toward the emulsion oxidations. Boo *et al.* reported that gallic acid use has unremarkable antioxidant effect after addition to the o/w emulsions of sunflower [33]. Farhoosh *et al.* observed that gallic acid has higher antioxidant activity in oils than its effect in the emulsions, indicating the important role of the carboxyl group, in addition to the effects of unsaturation degree of lipids in gallic acid antioxidant effect [34]. Pittia *et al.* showed that gallic acid plays an important role in the stabilization of colloidal properties of o/w emulsions, while it showed a lower effect against the oxidations [35].

However, Wu *et al.* reported clear antioxidant activities of gallic acid with its ester using o/w emulsion in the next order of antioxidant effect: stearyl $<$ gallic acid $<$ octyl $<$ lauryl $<$ propyl gallate [36].

In new research by Zhou *et al.* gallic acid or its esters were used together with tocopherol using o/w emulsions. They observed these esters exhibit antioxidant effects that shared with tocopherols, knowing that propyl gallate showed the highest synergistic effect [37]. In other studies, the improvement in the antioxidant activity of esterified gallic acid derivatives is also observed in the double emulsions using encapsulation [38]. Gallic acid and its derivatives showed a wide range of beneficial effects in inhibiting and/or managing several disorders, also their suitable stability and safety profiles, make them significant options to be introduced as dietary supplements.

2.3 Rosmarinic acid

Rosmarinic acid is a caffeic acid ester, found as a major phenolic compound in many genera of *Lamiaceae* that includes: *Origanum* spp., *Rosmarinus officinalis*, *Salvia officinialis* and Perilla [39,40]. Different researchers reported rosmarinic acid as major phenolic acid of different cooking herbs (e.g. rosemary, thyme, sage, and oregano) in a concentration range of 0.052 and 25 gm/kg of the dried plant [41,42]. Moreover, Choulitoudi, *et al.* indicated an amount of 19 gm/kg in the pink savory leaves [43].

Recently, a study has shown the antioxidant effects of rosmarinic acid in o/w emulsion based on corn oils and stabilized by different emulsifying agents [44]; TBE that prepared using soybean oil or linoleic acid [17][45]. Berhow *et al.* added both pure rosmarinic acid and its rich extracts (using common sage leaves), with about 30 mg/gm into o/w emulsion, the result showed that the treatment was very efficient as an antioxidant. [46]. There is a lack of connection between studies, and several gaps are yet to be filled to confirm the role of rosmarinic acid in human health. In future studies covering rosmarinic acid, the application of the findings created during laboratory or preclinical study for developing trials and studies in humans.

2.5 Carnosic acid

Carnosic acid is one of the important diterpenes found in various Lamiaceae spp. [47]. The common sage contains about 1.5 to 2.5% of carnosic acid in the dried leaves [48]. Carnosic acid is used as a food preservative, as well as a preservative in other products, like mouthwashes, toothpaste, chewing gums, due to its antimicrobial and antioxidative characteristics [49]. Carnosic acid was shown to have a clear activity against the oxidation of emulsion, which was improved at 5 pH [50]. Additionally, several researchers used rosemary extracts and other extracts of Lamiaceae plants in emulsions and ascribed their activities against action mostly to carnosol and carnosic acid [51,52]. Newly, Tang, *et al.* have established a microemulsion using E-vitamers in order to improve and stabilize the carnosic acid antioxidant effect and thus developing a new system for possible application in bioactive mechanisms [53].

Generally, though this lipophilic compound is recognized for its strong antioxidant actions that allowed various trading uses in beverages and foods, its mechanism of activity toward the emulsion oxidation haven't been totally elucidated [54].

2.6 Ferulic acid

Ferulic acid is one of the well-known phenolic acids, which present in the seed of orange, apples, coffee, artichoke, and groundnut [55]. Flaxseed is considered the richest herbal source of ferulic acid of about 3.5 gm/kg [56]. Black beans are considered a rich natural source, which contains about 0.8 gm/kg of ferulic acid [57,58]. Furthermore, ferulic acid can be present in tomatoes and in Brassica vegetables [23]. Some of evidence are available for establishing the antioxidative activities of ferulic acid in different o/w models involving Tween, corn oils, and linoleic acid emulsion [59][17], as well as Tween-menhaden emulsion [60]. In recent times, Jeong *et al.* mentioned that the decarboxylated product of ferulic acid (4-vinyl guaiacol) has a high antioxidant effect when combined at 198 ppm with 9% o/w emulsions for fifty days [61]. However, Bosc *et al.* reported that ferulic acid hasn't any antioxidant effect in o/w emulsions that contains a high amount of omega-3 fatty acid [62]. No acute or chronic side effects of ferulic acid ingestion or topical application have ever been reported. Therefore, increasing evidence for its health benefits is promising to encourage future clinical trials.

2.7 *p*-Coumaric acid

Numerous herbs and microorganisms have been considered to be rich in *p*-coumaric acid, like fungus, tomatoes, peanut, basil, navy bean, garlic, and carrot [63]. *p*-coumaric is found in most cereals and fruits (especially berries and pears) [23,64], and in honey at a range of 1.7–4.7 mg/kg [65]. Clytra rotunda and Halodule pinifolia are also considered to be a rich source of *p*- coumaric acid, which can be considered to be a reason for their obvious biological activities [66]. The study clarified that *p*-coumaric acid is found in high concentrations in some mushrooms [66]. Additionally, some researchers observed that *p*-coumaric acid is found in the extract derived from stem and leaves of Amaranth at 27–45 mg/kg [67,68]. Kim *et al.* recognized *p*-coumaric acid as a major phenolic compound found in the Hordeum vulgare water extract [69].

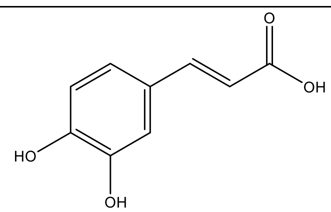
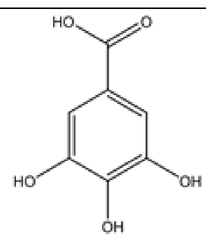
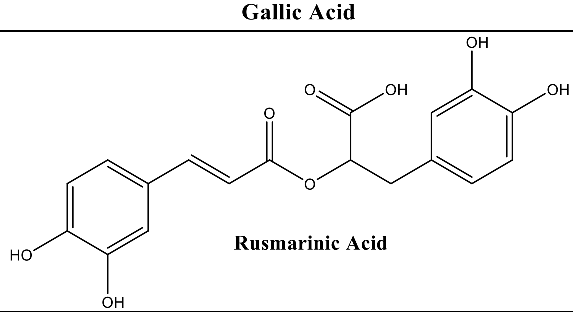
Nowadays, some researchers have engrossed in the antioxidant effects of *p*-coumaric acid [70], and its identifications in different natural origins [71]. Newly, Gim *et al.* used NMR and HPLC analysis of ethanolic and aqueous extracts of baked hulls of rice and detected *p*-coumaric acid, vanillic acid, and ferulic acid as the prevalent phenolic substances. The researchers noticed that the extracts of baked rice hulls, which contain a high amount of *p*-coumaric acid, sheltered from the oxidation of o/w emulsions [72]. However, further studies are needed to check the safety concerns on roasted rice hulls, which can help to expand the utility of rice hulls as valuable ingredients in bioindustry.

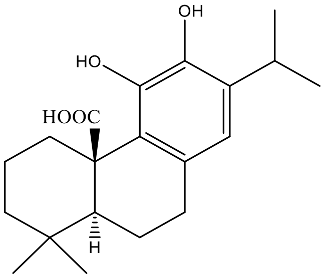
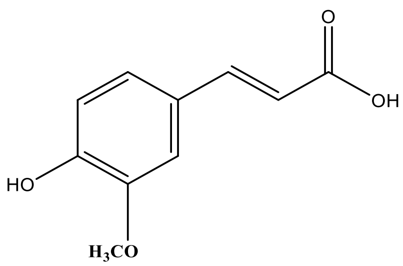
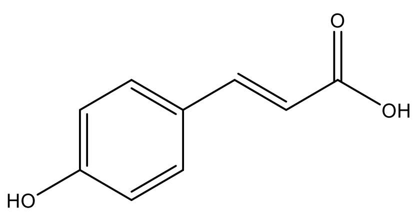
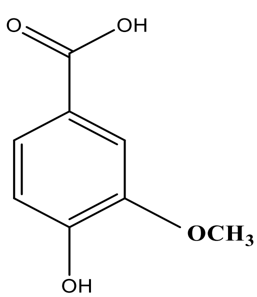
2.8 Vanillic acid

Vanillic acid (bihydroxybenzoic acid derivatives) is frequently utilized for flavoring purposes [73]. It is present in some fruit, cereal grains, and olives, as well as in cider, beer, and wine [73,74]. Soh *et al.* in 2019 identified the major phenolic components in potatoes and quantified vanillic acid at a concentration range of 0.02-0.04 gm/kg[75]. Inchingolo *et al.* analyzed red propolis extract and reported vanillic acid as a major phenolic compound[76].

Vanillic acid was also presented in the extract of Euterpe oleracea [77] and was detected in the roots of Angelica sinensis at a concentration range of 1.1-1.3 gm/kg [78]. Moreover, Dianat *et al.* reported that vanillic acid is found in different herbal origins like *Juglan riegia, Cheniopodiastrum muraile, Melilotus messanensis, and orchardgrass*[79]. Cuvelier *et al.* reported a high antioxidant character of vanillic acid during oxidation of TBE, at pH 3.4 [80]. Moreover, the antioxidant effect of vanillic acid-grafted chitosan (v-g-c) throughout the microencapsulation of unsaturated fatty acid of fish oil in the emulsion. After 30 days of storage, decreased peroxide values confirmed good encapsulation efficiency and oxidative stability of v-g-c [81]. In vivo bioactivity of this new functional food ingredients (v-g-c) needs to be evaluated in future. The following table (table 1.1) illustrates the natural sources, structures and amounts (g/kg of dried plant) for some of herbal phenolic acids.

Table 1.1-Chemical structures of herbal phenolic acids and their quantities in the natural sources

Structure of phenolic acid	Natural sources	Quantities (g/kg)	Reference
 Caffeic Acid	Blueberry	1.47	[25]
	Coffee	0.9	[25]
	Mango	1.00-1.76	[73]
	Banana	0.23-0.31	[73]
	Yerba mate	1.50	[21]
	Eucalyptus globulus	2.0-2.9	[24,82]
 Gallic Acid	Mango	11.45-34.49	[73]
	Banana	1.10-1.24	[73]
	Chestnut	3.50-9.10	[23]
	Berries	0.03-0.09	[23]
	Black tea	0.8	[32]
 Rusmarinic Acid	Rosemary	0.16-12.86	[41,42]
	Oregano species	0.05-25.63	[41,42]
	Sweet basil	10.86	[42]
	Salvia officinialis	1.18-21.86	[42]
	Pink savory	19.50	[43]
	Thyme	0.08-6.81	[41,42]

 Carnosic Acid	Salivia species	0.1-21.7	[54]
	Rosemary	40-100	[54]
	Sage leaves	15-25	[48,53]
 Ferulic Acid	Artichoke	2.75	[55,82]
	eggplant, redbeet, spinach, peanut, grapefruit and orange	0.07–0.35	[56]
	Banana	0.49–0.53	[73]
	Beans	0.8	[53]
	Mango	0.75	[73]
	Flaxseed	4.10	[56]
	Cereal grains	Up to 2	[83]
	coffee	0.09–0.14	[56]
	Acai oil	0.10	[74]
	Cell wall of grain	13.52–33.11	[55,84]
 p-Coumaric acid	Strawberries	1.11	[23]
	Mango	0.90	[73]
	Pears	0.01–0.46	[64]
	Banana	1.06	[73]
	Onion peel	0.58	[64]
	Peanut	1.04	[23]
	Honey	0.002–0.005	[65]
	Red amaranth	0.028–0.042	[68]
	Mushrooms Traces	Trace-3.70	[66]
	Berries	0.01-0.95	[23,64]
 Vanillic Acid	Banana	0.12–0.37	[73]
	Acai	0.002	[77]
	Mango	0.47–3.76	[73]
	Potato tuber	0.02-0.04	[75]
	Angelica sinensis	1.1–1.3	[78]

3. Biochemical characteristics and health effect of phenolic acids and their herbal extract

The 2nd part of this review provides an outline of many natural origins for various phenolic acids but also reviewed many studies that exposed their obvious antioxidant properties against the oxidation of lipid in emulsions. The review showed that the emulsion might provide a valuable system as a model for more investigations of phenolic activities in interfacial biological system.

3.1 Common health features of herbal phenolic acids

This part highlighted the major manuscript goal providing a summary of the newest literature that related to the healthiness characteristics of the studied phenolic acid. In addition, many kinds of research have been reviewed into phenolic acid individually and as a mixture of herbal extract. The evidence of research body highlighting the effects of several phenolic acids against different tumors and their major actions (e.g. free radical scavenging, enzymes induction, repair of DNA damages, apoptosis, and cell proliferation [85].

Silva *et al.* showed that phenolic acids are considered one of the important sources of treatment of various cancers, focusing on human colon cancer [86]. Jayachandran *et al.* reported the possessions of phenolic acids to enhance glucose with lipid profile that linked to pathologic situations (e.g. DM, cardiovascular disorders, etc.) [87]. Phenolic acid-rich diets have been reported to prevent some allergies and slow the progress of Alzheimer's disease [88].

3.2 Caffeic acid

Caffeic acid demonstrates significant antioxidant and antimicrobial activities [89]. In addition to its evident anti-aging and antioxidant effects, caffeic acid was found to be effective in treating different dermatological disorders [90]. Porto *et al.* formed a drug-delivering system depended on o/w emulsion with microparticle loaded with caffeic acid, in order to confirm a prolonged caffeic acid delivery to the target cells and thus treat the hair follicle inflammation [91]. Likewise, Santos and Paulo incorporated caffeic ethyl cellulose as micro-particles in several dermatological products and examined if these microparticles have an anti-aging effect [92]. Moreover, recent research has proved that the natural compound, caffeic acid phenyl ester (CPE) has anticancer effects [93]. The caffeic acid chemical structure is believed to intensely account for the antioxidant activities of this compound, which link to some anti-cancer properties [93].

Recently, incorporation of caffeic acid and CPE in the diet rats, with a subcutaneous dose of 5 mg/kg or oral dose of 21 mg per kg, showed to prevent the cancer progression in HepG2 and decrease the invasive activity of tumor throughout the liver [94]. Furthermore, recent clinical research has proved a strong chemoprotective outcome of CPE with its analogs at a dose of 21 mg per kg, against lipid oxidation and propagation of liver cancer cells in rats [95].

Chen *et al.* utilized ester of sucrose and fatty acids to nanoparticles of CPE in an aqueous solution of propylene, the results showed that these nanoparticles improved the cytotoxicity of CPE against HCT-116 (colon cancer), and MCF-7 cells (breast cancer) [96]. Another medical research [97] showed the preventive activity of CPE products toward the cholinergic enzymes that play a role in the mechanism of Alzheimer’s disease development. Caffeic acid with its derivatives, such as CPE, have been shown to act against HCT-166 by their cytotoxic action to the cancer cell but not to the normal one [98]. Additionally, Wang *et al.* examined the action of caffeic acid at a dose of 100 mg per kg on structure modifications produced by a liver tumor in rat microorganisms. The researchers recognized that caffeic acid decreases some biomarkers, which indicate hepatic injury [99].

3.3 Carnosic acid

Because it can be extracted from different natural origins (e.g. Rosmarinus and Salvia spp.), in addition to its proved antioxidant and functional properties, carnosic acid has been incorporated in various pharmaceutical applications [53,55]. Several studies highlighted the protective effect of carnosic acid against liver diseases. In a recent experimental trial for weight loss and decreased visceral adiposity, male mice with nonalcoholic-fatty liver disease, feed with carnosic acid for five weeks in comparison to placebo, the researchers established that carnosic acid could be used for developing a novel drug for treating the NFLD [100]. Lin *et al.* reported the liver toxic effect of carnosic acid at a concentration range of 3-10 M in man microsomes and hepatocytes [101]. While carnosic acid didn’t exhibit significant inhibition of enzyme at 4 M, it augmented enzyme effect at 10 M, in comparison with rifampicin and phenobarbital drug [101]. The outcomes showed possible interactions of carnosic acid with drugs, thus the appropriate safety should be established before further use of carnosic acid as a supplement for weight loss [101].

Shlyonsky *et al.* reported that carnosic acid can offer protection from chronic neurodegenerative diseases, such as Parkinson’s disease, by an action that is linked to the transcription activation of intrinsic defense mechanism against any oxidative stress (NRf2/ARE pathway) [102]. Wu *et al.* using in vitro trials in cancer cells from human breasts have detected that a dose of carnosic acid 20 g/mL prevents estrogen receptor-(-ve) breast cancer by apoptosis activation and expression of antioxidant genes[103]. A recent study established an important antiinflammatory effect of carnosic acid shared with tomato extract that is rich in lycopene and astaxanthin [104]. However, Vossen *et al.* didn’t report any action of carnosic acid against oxidation of protein and lipid using in vitro sensitized gastric digestion type model [48]. These studies showed that carnosic acid possess powerful antioxidant, anticancer and anti-inflammatory effects, and these effects are depend on the environmental conditions (e.g. gastric content).

3.5 Gallic acid

In 2017, researchers had mentioned neuroprotective, and anticancer and heart-protective characteristics of gallic acid that is mostly ascribed to its antioxidative properties toward free radicals signaling network [105]. Pourgheysari *et al.* mentioned that gallic acid induces apoptosis in lymphoblastic leukemia (LBL) cells and inhibits their proliferation, the results showed that gallic acid result in a remarkable decrease in the cell growth in 72 hours and an IC50 of about 60 µM in 24 hrs, about 50 µM in 48 hrs and about 30 µM in 72 hrs. [106]. Recently, gallic acid showed potentiate the antitumor activity of chemotherapeutic agents (e.g., Carboplatin, Paclitaxel) using HeLa cells [107]. The authors detected that the co-treatment of Paclitaxel with gallic acid might be a promising substitute with fewer side effects than a combination of Paclitaxel and Carboplatin in cervical cancer treatment [107]. Recent pharmacokinetic animal and human studies that depend on Chinese gallic acid-based medicines were reported but more investigations are needed on gallic acid kinetic profile before concluding its efficiency toward various pathological disorders [108]. Curti *et al.* studied gallic acid potential as a new promising antitumor, the researchers treated the glioblastoma cell line (T98G human cell) for 24 hr with a range of gallic acid concentrations of 1 to 100 gm/mL [109]. Accordingly, gallic acid exerts an anti-proliferative and protective effect on T98G cells by epigenetic regulation (dose-dependent) mediated via miRNAs [109].

Mazzini *et al.* performed an experimental study on rats with myocardial infarction using an oral dose of gallic acid monohydrate at 50 and 100 mg/kg [110]. They detected that the myocardial infarction modified the pharmacokinetic properties of gallic acid and hence regulate its possible activities [110]. Likewise, Palacios *et al.* reported that gallic acid can shows -ve inotropic and chronotopic effects in myocardial damage induced by isoproterenol [111]. These studies proved that gallic acid has strong antioxidant activity which leads to its anticancer effect.

3.6 Ferulic acid

Recently, many clinical types of research have confirmed that ferulic acid has in vivo antioxidative activity by hunting ROS and improving the response for cell stress via the upregulation of the cytoprotective system [83,112]. According to its anti-inflammatory and antioxidant activities, ferulic acid is a phenolic substance that has preventive effects from a number of pathological disorders like cancers, cardiovascular diseases, skin problems, and diabetes mellitus [113]. Martadi *et al.* reported the beneficial effects of ferulic acid for health and observed its preventive function from neurotoxic effects depended on many in vivo and in vitro studies [83]. Gim *et al.* treated rats (males, 0.210–0.230 kg) with ferulic acid (100 mg per kg) and detected an obvious neuroprotective role [114]. These findings endorse the ferulic acid use for the development of drugs against many neurodegenerative problems, although some questions should be opened before the clinical advance and application of ferulic acid in patients.

Ghosh et al. performed an experimental study, which included oral administration of ferulic acid to diabetic rats (50 mg/kg, for two months). The researchers showed the preventive effect of ferulic acid from the cellular stress that induced by streptozotocin in the heart tissue [115]. Bachmair *et al.* mentioned a strong preventive effect of bihydroferulic acid from platelet activation [116]. Agilan *et al.* reported that ferulic acid (10–40 gm/mL) prevents the UV light at 290–320 nm that can result in oxidative damage to the DNA of dermal fibroblasts [117]. The same authors found by an experimental study that ferulic acid (180 mg/cm2 over 7 months) protected the mice's skin from carcinogenesis that induced by chronic exposure to UVB light [118]. Campisi *et al.* performed a population-dependent case, a control study to test the effects of phenolic acids consumption on prostate cancer. Between 2044 individuals, 119 cases of prostate cancer were collected. The multivariate logistic regression indicated that both p-coumaric acid and ferulic acid were related to decreased risk of prostate cancer [119]. Several studies proved the antioxidant, anticancer and neuroprotective effects of ferulic acid in vitro. Future clinical studies are recommended, to be incorporated in the food supplement products.

3.7 *p*-Coumaric acid

p-coumaric acid has been studied to reduce LDL oxidation and has antimutagenic, antimicrobial, antigenotoxicity effects [120]. Newly, Victorelli *et al.* reviewed certain biochemical characteristics of *p*-coumaric acid (including tumor suppression and radical scavenging activities) that are associated with its pharmacological effects[121]. Boo in 2019 focused on the antimelanogenic effect of *p*-coumaric acid by testing its preventive effect from the synthesis of melanin as detected in the epidermal melanocyte of humans [122]. Rasool *et al* [123] reported that dietary *p*-coumaric acid could interfere with the formation of osteoclast alleviating rheumatoid arthritis, which was also reported by Trisha [63].

Pei *et al.* reviewed *p*-coumaric acid with its conjugates focusing on biological activities and dietary sources [64]. The researchers reported that upcoming researches should be focused on pharmacokinetic possessions of *p*-coumaric acid for promoting its use in the diet and cosmetics [64.]. Krogh *et al.* used Caco-2 cells, which were treated with a dose of 150 M of *p*-coumaric acid for 24 hr and observed protective effects against the colon cancer development via retarding the progression of the cell cycle [124]. Arumugam *et al.* concluded that *p*-coumaric acid increased the glutathione level in the diabetic rat liver inhibiting oxidative stress development [126]. Moreover, Spencer *et al.* compared the neuroprotective effects of different phenolic agents using cortical neuron cultures of a mouse [127]. The researchers observed protective effects of *p*-coumaric acid at a concentration of 1 mM stronger than carnosic acid and gallic acid effects [127]. Recently, Nevin *et al.* concluded that p-coumaric acid protects H9c2 (2-1) cells from cardiotoxicity that induced by doxorubicin [128]. These studies indicate multi effects of *p*-coumaric acid (e.g. antioxidant, anticancer, neuroprotective and cardioprotective) which is need more clinical studies to find its functional role in many products.

3.8 Rosmarinic acid

Rosmarinic acid is an important component of the leaves of several plants (e.g. *Rosmarinus officinalis, Salvia officinalis, Perilla frutescens, Mentha arvense* and *Ocimum basilicum*) and has neuroprotective, anti-microbial, anti-oxidant, and anti-cancer effects [129]. Bae *et al.* studied the preventive effect of rosmarinic acid on box1 that induces response to injury and infection [129]. Chuang *et al.* concluded that rosmarinic acid can significantly suppress IL-8 production and TNF-a, as a result it inhibit the inflammatory responses induced by propionibacterium[130]. Regarding the anti-inflammatory mechanisms, Yang *et al.* reported the down-regulation of protein c receptors (an important receptor that plays pivotal roles in coagulation and inflammation) caused by rosmarinic acid, in vitro as well as in vivo [131]. Rossi *et al.* investigated whether rosmarinic acid at a dose range of 0.01–0.10 mg/mL can offer protection from ciguatoxin-induced cytotoxicity in the primary neuron of humans [132]. The authors observed that the pretreatment with rosmarinic acid at a concentration of 0.01 mg/ml has neuroprotective effects, resulting in a significant reduction in ciguatoxin-induced extracellular LDH action, NAD decline, as well as DNA damage, in comparison to the cells treated with ciguatoxin alone [132].

Sarmento *et al.* noted that rosmarinic acid displays many beneficial effects for health (including anti-carcinogenic and antimicrobial properties) depending on its dose and bioavailability [133]. Rahman *et al.* have focused more specifically on the anti-carcinogenic characteristics of rosmarinic acid proposing several anticancer mechanisms of including antioxidant activity in addition to apoptosis and proliferation of tumor cells [134]. Stanbury summarized the clinical studies that have shown rosmarinic acid effects against the allergic immunoglobulin, as well as its effects toward the inflammatory response of leukocytes, thus being effective for treating allergic disorders [40]. Farag *et al.* have also reported the action mode, in addition to the health benefits of rosmarinic acid [135].

Marchesi *et al.* reported that rosmarinic acid has a protective effect from acute hepatic injury in the intoxicated rats via employing some antioxidant, anti-apoptotic and anti-inflammatory effects [136]. Lately, Afonso *et al.* studied the protective activities of rosmarinic acid from DNA damage induced by ethanol in mice, which observed an obvious antigenotoxic capacity at a dose of 100 mg/kg [137]. Olaciregui *et al.* concluded that rosmarinic acid at a concentration of 105 M enhances the functions and in vitro sperm fertilizing capability of boars by preventing oxidative stresses throughout cryopreservation [138].

Moreover, Namasivayam *et al.* studied the molecular mechanism that is responsible for the chemopreventive effect of rosmarinic acid from colon tumors in the rat, the researchers stated that supplying rosmarinic acid with a dose of 5–20 mg per kg this sheltered rats from harmful effects that result from colon carcinogenic 1, 2-dimethylhydrasine [139]. These studies of the last decade showed several beneficial health effects of rosmarinic acid (e.g. hepatoprotective, neuroprotective, anti-carcinogenic, antimicrobial, and anti-inflammatory), which opened the door for its use in pharmaceutical industries.

3.9 Vanillic acid

Vanillic acid has been described to discuss some health valuable effects, via anticancer antioxidative, anti-inflammatory, neuroprotective, and antimutagenic effects [140,141]. Radmanesh *et al.* fed a set of ten rats for 240 hrs with vanillic acid with 0–10 mg per kg, the outcomes showed a clear activity of vanillic acid against the hazard of heart failure [79]. Similarly, Hamzavi *et al.* demonstrated the efficiency of vanillic acid against peroxidation of lipids, indicated by a reduction of malondialdehyde, and antioxidant enzymes enhancement, in isolated hearts of rats treated with ischemia-reperfusion [142]. Hong *et al.* following experimental studies in rats stated the valuable effect of vanillic acid in treating ulcerative colitis [143]. Cinkilic *et al.* examined the possible activities of vanillic acid toward the genomic damage induced by mitomycin C in a human lymphocyte in vitro. Remarkably, vanillic acid at 1.0 g/mL, showed a significant decrease in DNA injury, and at a high dose (2.0 g/mL) showed genotoxic actions on DNA [144]. On the other hand, Ristica et al. stated that vanillic acid at a concentration of 2 M didn't significantly reduce the activation of platelets biomarkers of cardiovascular disorders [145].

In an experimental study by Singh *et al.* five sets of mice were used as control and the others were treated as an active group that was supplied with vanillic acid at 5–100 mg per kg for 30 days [146]. The outcomes presented that vanillic acid at doses of 50 and 100 mg per kg enhanced the habituations memory, reduced the cortisone, acetylcholinesterase, and augmented the antioxidative effect of mice [146]. Additionally, Pagotto *et al.* stated the antimicrobial activity of vanillic acid depends on the pH range, which was shown to prevent bacterial growths and high-temperature resistance of Cronobacter [147].

This deduction can lead to new applications of vanillic acid in the storage of foods [148]. Many studies showed different effects of vanillic acid especially as neuroprotective, this can paves the way to future studies about vanillic acid to be used as an ingredient of functional food and as a food supplement for inhibition of neurologic complaints.

3.10 Herbal extracts as phenolic acids mixtures

Nature has provided a great number of plants like rosemary, thyme, mint, sage, oregano, which contain a high amount of phenolic acids with powerful antioxidative and antiinflammatory possessions [149,150] that protect DNA against oxidative damages [151]. Bael flowers that contain high concentrations of p-coumaric acid, carnosic acid, and vanillic acid, as well as holy basil seeds, which are rich in gallic acid and p-coumaric acid, have been shown to possess powerful antioxidative properties against DNA damages [152,153].

New research found that phenolic acid-rich extracts can exert an obvious cardioprotective effect by modulating the platelet function [154]. Geetha *et al.* reported hypolipidemic and anti-obesity effects of hydroalcoholic avocado fruit extract (mainly rich in gallic acid and vanillic acid) in rats that fed with fatty diet[155].

An extensive study by Gogia *et al.* has been reported in the past years concerning various rosemary extracts, which are predominantly rich in rosmarinic acid and carnosic acid [156]. The study showed that rosemary extract offers protection of Jurkat cells against oxidative stress caused via hydrogen peroxide [156]. In a recent study, Barrajón-Catalán *et al.* examined the anticancer effect of rosmarinic acid by its efficiency to prevent several types of cancer progressions and metastasis[157]. Tracee et al. reviewed different features of rosemary extracts by testing their beneficial health effects and toxicology [158]. Recently, Mena *et al.* demonstrated that rosemary extract has an anti-tumor effect through cell death initiated by ROS [159]. Garcia *et al.* reported a clear preventive role of rosemary extract against colds, rheumatism, as well a pain of joints and muscles [160]. A recent review in 2019 showed the prophylactic and therapeutic effects of rosemary extract (in vivo/in vitro) on certain physiological problems initiated by different biochemical compounds [134]. Tsiani *et al.* reviewed the biologic and antitumor activities of *R. oiffcinalis*, the authors recommended future in vivo animal studies to find the doses to be administered; the best administration route; the plasma levels of CA, RA and other RE bioactive ingredients; the affected signaling pathways; and any possible toxic effects related to chronic administration [161].

Furthermore, p-coumaric acid-rich alcoholic extracts of pendant amaranth and of *A. spinosus* extracts showed significant peripheral and central anti-nociceptive potential as well as anti-inflammatory activities in the mice model [39]. Phan *et al.* detected obvious therapeutic activities of phenolic mixture that containing gallic acid, p-coumaric, ellagic acid, and others against lung cancers [162]. The derivatives of hydroxycinnamic acid obtained from mulberry fruit were observed to enhance the ROS creation by working as prooxidants, thereby killing the tumor cells [163]. Policarpi *et al.* stated that the aqueous extract of pecan nut that is rich in gallic acid, caffeic acid, and vanillic acid showed a clear inhibitory effect on the MCF-7 cell line of breast cancer, and also against the tumor progression in Balb-C mouse [164]. Beara *et al.* reported an overview on some beneficial biological effects of the wild onions, which are principally rich in many phenolic acids [165].

The same colleagues have reported that an alcoholic extract of yellow onions that is rich in different phenolic acids (e.g. ferulic acid, p-coumaric acid, caffeic acid, and vanillic acid, can show selective inhibitory activity against colon adenocarcinoma and cervix epithelioid cancer [166,167].

4. Conclusion and upcoming dares

Depending on the investigation about this review concerning the biochemical actions of different phenolic acids (in vitro/in vivo), the authors established some conclusions and recommendations for upcoming investigation, which include:

4.1 Phenolic acids effects in emulsion

Recently, a growing number of researchers described the well-recognized antioxidant effects of natural phenolic acid in o/w models. Outcomes of the new researches on the antioxidative effect of phenolic acids in different emulsion products might propose a base for innovating visions in an inclusive scope of cosmetic and food products.

By regulating the interfacial concentration of antioxidants in o/w emulsion could be considered as a rational method for monitoring its action toward lipid oxidations. The additional effort of this field concentrates on assessing the distribution constant of phenolic acid in the emulsion as an aspect that could further monitor and elucidate its antioxidative efficiency in the interfacial system.

Future trials may involve developing nano-emulsion systems to permit phenolic acid delivery and thus encourage their application in food supplements and even in various drug products.

4.2 Beneficial health characteristics of phenolic acids

This review reported an overview of the latest clinical studies (mostly experimental) concerning phenolic acids. The results propose satisfactory evidence for supporting the investigated phenolic acids, during their food supplementations, which showed protecting effect from an inclusive range of problems as infections, cancer, cardiovascular, neurodegenerative, and inflammatory disorders.

The phenolic acid mixture has been shown by the newest study evidence to have many valuable health properties. The potent antioxidant activity of the natural herbal preparation may be more precisely related to the synergism effects between their phenolic constituents.

Though some of these phenolic acids are effective bioactive diet components, the metabolic and pharmacokinetic characteristics are not completely revealed. This reason limits their therapeutic uses and requires additional clinical studies for supporting and optimizing their future pharmaceutical and nutritional applications.

Conflict of interest

No information.

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