Trakia Journal of Sciences, No 4, pp 267-282, 2022

Available online at:
http://www.uni-sz.bg

ISSN 1313-3551 (online) doi:10.15547/tjs.2022.04.001

Original Conrtribution

ANTIOXIDANTLY-MODULATIVE, CHEMOPREVENTIVE AND ANTI-SARS-COVID 19 ACTION OF MEDICINAL PLANTS

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ABSTRACT
PURPOSE: In the last 20 years, the demand for effective universal natural chemoprotectants and radiomodulators has increased. In this article, we provide evidence for the antioxidant and protective nature of herbs and their potential to be used as nutritional antioxidants, DNA modulating agents, metabolic radiation scavengers, immunomodulatory agents of SARS-COVID-19 infection, hepatoprotectors. The main action of natural antioxidants (Silybum marianum, Curcuma longa Linn, Haberlea rhodopensis Friv, Tinospora cordifolia (Willd.), Lemna minor Linn., Sambucus nigra Linn.) is carried out by capturing free radical structures, signaling redox modulation, compensating of oxidative disturbances, regulation of cell proliferation. Future development of effective herbal combinations with conventional chemotherapeutics, neutralizing systemic oxidative stress and predisposing to a reduced risk of developing cardiovascular, pulmonary and neurodegenerative diseases, cancer, etc., is necessary.

Key words: herbs, medicinal plants, antioxidants, chemoprotection, SARS-COVID-19 infection

INTRODUCTION

Over the recent decades, the interplay between herbal medicinal plants as preventive agents for the treatment of various diseases increasingly gaining popularity. Today plant antioxidants are seen as potential agents for the prevention and therapy of various diseases; there is no side effect as in the case of synthetic agents (1). The most common causes of traditional herbal/plants remedies are for the treatment of chronic conditions and their perception as natural, safe and non-toxic (2). Herbal plants after treatment are taken as teas, syrups, essential oils, powders, capsules, and tablets. Each tablet contains a dry or powdered form of raw herbs or dried extract. The herbal or plant extract is extracted by alcohol tinctures, hot water extract, long-lasting boiled extract, root potions, etc.

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Medicinal plants as preventive agents from traditional medicine

The common practice in the use of herbs is observed in Chinese and Indian (*Ayurvedic Pharmacopoeia*) traditional medicine using more than 1000 plant species (3). Herbal and plant extracts, and teas are highly effective against common diseases like: cold, fever, hyperactivity, ulcer, cough, gastrointestinal problems, dysentery, liver disease, urinary tract infection, arthritis, bronchial asthma. They have a noticeable effect in cancer treatment, chronic cardiovascular, anti-inflammatory, and kidney diseases (4-6). Investigations from the last 20 years have suggested that herbal antioxidants could be useful to manage psoriasis, Alzheimer's and Parkinson's diseases, urinary tract infections, anemia, prostate enlargement, fever, allergic disorders, and also use of HIV/AIDS virus (7-9). Herbal antioxidants of plant origin consist of primary and secondary metabolites, have unique biological properties. The ability of herbal and medical plants to act simultaneously against various diseases and oxidative changes in the body makes them extremely effective for medicine. Herbal drugs, dietary ingredients, and edible plants, including silymarin, curcumin, perillyl alcohol, green tea, epigallocatechin gallate, carnosol, carotenoids, genistein, resveratrol, soy isoflavones, oleanolic acid (6), gingerol, catechins, isoflavones, eugenol, isoeugenol, isothiocyanates, lycopene, phytosterols, vitamins, beta carotene, and flavonoids, used in medical applications, act as chemopreventive and cytoprotective agents and reduced damages of radiation exposure without treatment resistance and less toxicity (10).

This review focuses on herbs, medicinal plants and oils which are used directly for chemoprophylaxis, radiation efficacy and redox signaling pathways, but can also be used as dietary agents to protect against chemo-induced oxidative stress, cancer, and mycotoxicity.

Medicinal plants – the antioxidant potential of secondary metabolites, free radicals scavenging, and redox signalling

Plant extracts present as a collection of various phytochemicals, with powerful antioxidant activity, directly involved in the endogenous antioxidant defence system of the organism and redox signalling (11). Detection and isolation of ascorbic acid from medicinal plants (12) focused attention to the emergence and use of new plants, as agents for regulating or completely neutralizing the adverse effects of oxidative damages (OD) (13).

Herbal antioxidants are rich in various compounds with specific chemical and physiological characteristics. According to Khlebnikov *et al*., (14) antioxidants are substances, capable directly or indirectly to scavenge reactive oxygen species (ROS) or even prevent the production of free radicals. Antioxidants exist in various forms; most of them are secondary metabolites, including low or high molecular weight aromatic structures or oxygen-substituted derivatives (polyphenols, flavonoids, and tannins), terpenoids (carotenoids, sterols, plant volatiles) nitrogen containing alkaloids and sulphure containing compounds (15).

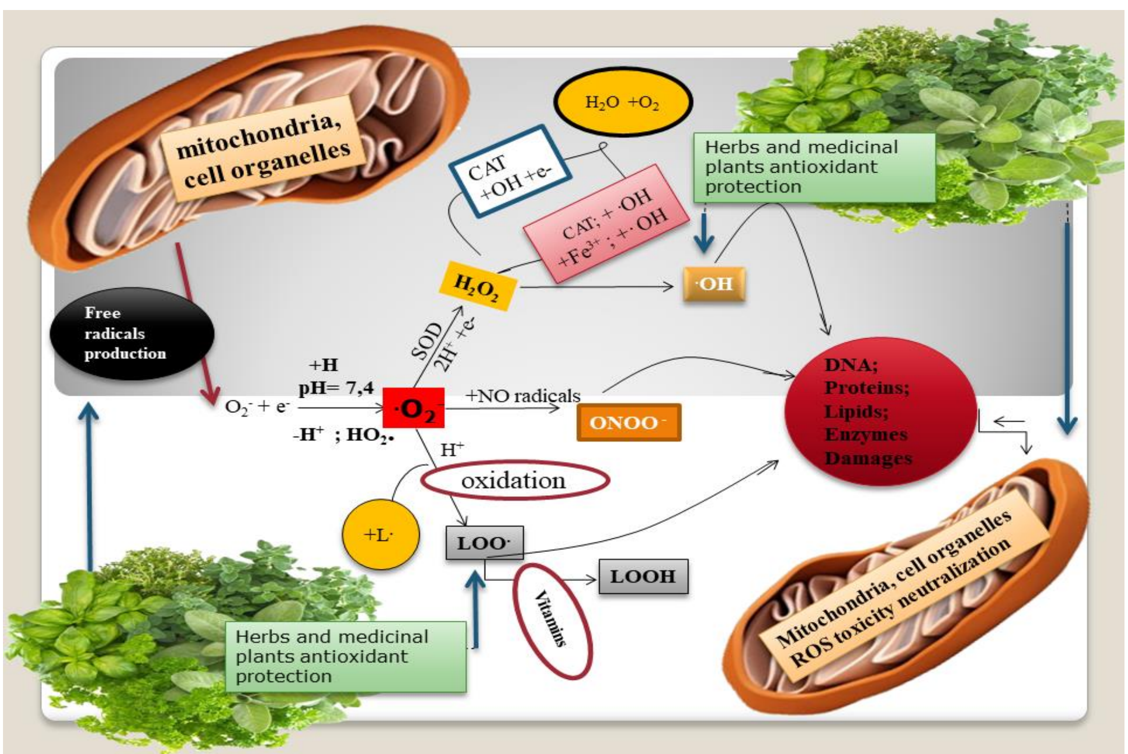

Figure 1. The delicate balance between free-radical production and herbs and plant antioxidants neutralization; Electron transfer, ROS, RNS and RSS radical toxicity neutralization (Adapted from Carocho and Ferreira, (17) and Kasote et al., (11)

The complex nature of plant antioxidants protects all parts of cells and tissues against oxidative damages and oxidative stress (OS) (16) while at the same time simultaneously destroying the harmful effects of ROS. In plant cells, maintenance of the balance between energy supply and control of ROS production is performed in chloroplasts, mitochondria, and peroxisomes. It is known that free radicals are atoms, molecules, or ions with unpaired electrons.

Considerably unstable electrons are active with respect to chemical reactions with other molecules. Simultaneously, with ROS production [include superoxide ($\bullet O_2^-$), hydroperoxyl (HO_2), hydroxyl (OH) radicals and other species like hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$)] in most of the cellular compartments, reactive nitrogen (RNS) species [include peroxynitrite ($ONOO^-$) and nitric oxide (NO•) radicals] and reactive sulfur species (RSS) were formed (17). Antioxidant active components and effective enzymatic and non-enzymatic systems of herbs and medicinal plants genetically support the planned free radicals production (6, 11). Neutralization of the extracted radicals and the ability to form the new stable radicals, due to intermolecular hydrogen bonding in further oxidation, is a typical property of antioxidants (18). Subcellular organelles of plants oversee the simultaneous free radicals-production but also to neutralize the toxic effects of their overproduction in **Figure 1.**

Based on the complex nature of low and high molecular weight natural antioxidants, it would be easy to characterize them as “redox buffers’’ or “redox signalling compounds” that play important roles in free radical metabolism and oxidation of biomolecules (19). Another major role of antioxidants is to modify the processes of mitosis, improve the process of OS (11, 20), and protect cells from aging. Espinoza *et al.* (21) report that increased vitamin E content reduces the harmful effects of environmental stress conditions in plants. Plant antioxidants have been shown to increase levels of GSH enzymes, glutathione, and also process of biosynthesis, absorption and recycling of ascorbic acid under abiotic and biotic loads. The accumulation of phenolic antioxidants leads to improved metabolism, radical protection from ultraviolet radiation, and an increase in enzyme-inhibitory properties (22). It has been found that ultraviolet stress (UV) and the ability of excessive UV-absorption increase the production of flavonoids (23) and tannins (24). Petra *et al.*, (25) report that the expression of secondary metabolites (flavonoids, alkaloids, and terpenoids) differ in their chemical structure is enhanced by various environmental oxidative signals, and possible of regulation through post-transcriptional and post-translational mechanisms.

Medicinal plants – preventive mechanism of action in apoplasts and antioxidant redox modulation

Low molecular weight antioxidants as well as secondary metabolites, contained in medicinal plants, buffered most of the cellular components, modulate ROS-antioxidant interaction and result in the normalization of the cellular redox balance (26). Prededova *et al.* (27) reported the electron emissions of plant molecules are accomplished through sequential oxidation and reduction processes, with the continuous decomposition of molecular oxygen. The initial formation of $\bullet O_2^-$ radicals results in the production or overproduction of complementary ROS. The antioxidant protection system responsible for metabolism is also responsible for ROS overproduction. Antioxidant cells deal with high levels of $\bullet O_2$, H_2O_2, and in some cases, $^1O_2$ (28). The synthesis of ascorbic acid at high concentrations reduced cytoplasmic thiols and thus tocopherols stably protected cells from further oxidation processes and act as hydrophilic and lipophilic buffers. The synthesis of hydrophilic and lipophilic antioxidants of medicinal plants and herbs is an important feature supporting homeostatic redox signaling (29). The internal mitochondrial membrane has always been considered as a space for the processing of generated mitochondrial ROS, oxygen molecules and OH radicals and a site for energy generation from the reduced electron carriers NAD^+, FMN and FAD (30). It was noted, at high levels of ROS production a significant portion of the oxidants ignore antioxidant protective systems and compromise important (30) mitochondrial functions. Foyer and Noctor (31) paid attention to the apoplast the area outside of the plasma membrane; there the first step is the ascorbate degradation as a low molecular weight antioxidant. The reduction levels of apoplastic oxygen to the •O_2^- radical are achieved through the absorption of the enzyme oxidase and is one of the main pathways for the production of ROS. The cytosolic and apoplastic superoxide dismutase (SOD) rapidly reduces and inactivates the highly toxic •O_2^- radical, converting it to H_2O_2 and O2. In parallel, apoplastic SOD simultaneously reduces NO radicals in cells (32). The apoplastic pathway facilitates the transport of water molecules and the free diffusion of solutions. Therefore, the antioxidant status of apoplasts as sites containing flavonoids and polyamines, as well as active and regulated ascorbate oxidase is of great importance (31, 33). Phenol compounds (quercetin, catechin, chlorogenic or caffeic acid) and molecular oxygen are electron acceptors in the apoplast. These reactions are important for metabolism and are critical in controlling ROS-mediated transmission of the signal, accumulated by various pathogens (31). Karpinska *et al*. (34) draw attention to the reduction state of apoplasts, which leads to the activation/ deactivation of protein sensors and the acclimatization of the herbs and plant leaves in **Figure 2.**

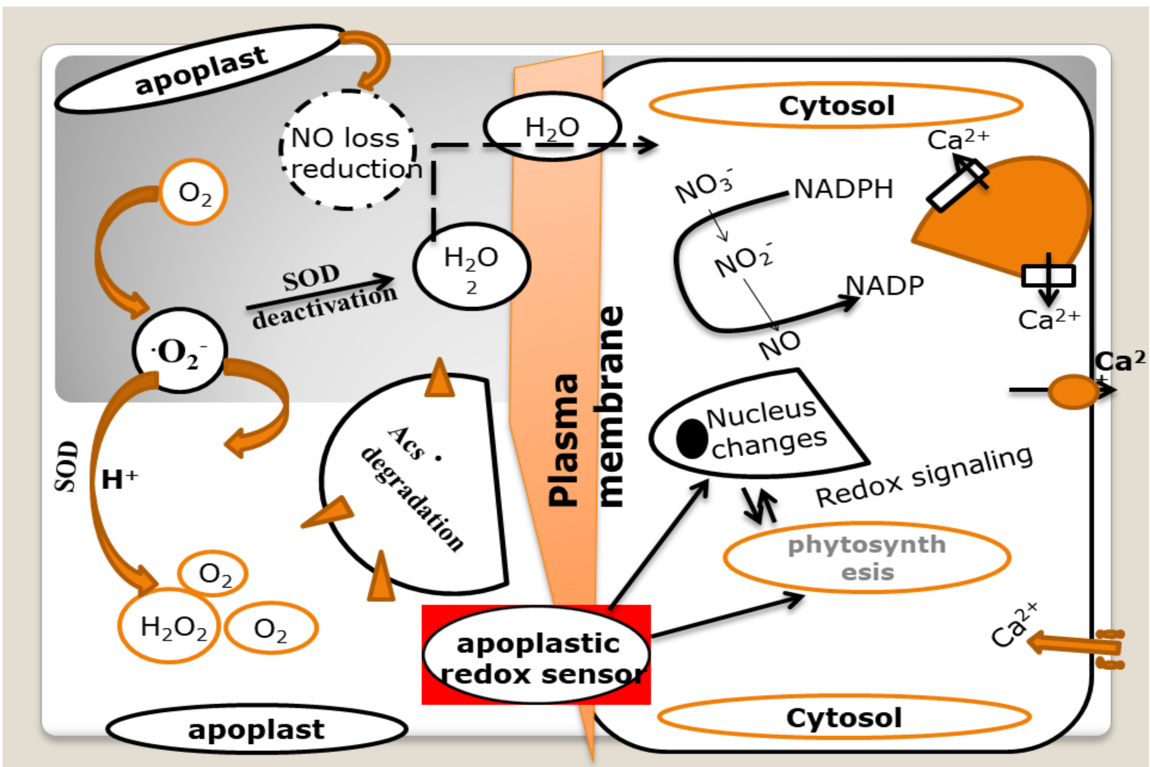

Figure 2. Detoxification pathways involved in the area outside of the plasma membrane: ascorbate degradation, reduction of apoplastic oxygen to the •O_2^- radical by enzyme oxidase uptake. Cytosolic and apoplastic SOD reduction and deactivation of •O_2^- and NO radicals in the cells (*Adapted from Karpinska et al. (34*).

The main reactive molecules (ROS), as a source of cellular factors of oxidative stress, oxidized DNA, lipids and proteins. Furthermore, at the physiological level, ROS has been seen as important signaling molecules involved in the transmission of intracellular signals to normal physiological processes and regulate gene expression. Excessive ROS production stimulates the activation of apoptotic and necrosis damages (35). Kreslevskii *et al.* (36) reported that induced oxidative stress conditions, activation of plasma redox systems and increased apoplastic ROS formation were typical concomitant processes.

Thiol oxidation in plants, may play an important role in ROS-mediated redox signaling. Foyer and Noctor, (31) demonstrated that directly or indirectly ROS oxidation in herbs and plants thiol-containing domains and various sulfur-containing species. Evolving plants have developed unique enzyme systems that effectively degrade NO and $ONOO^-$. Probably

NO as a free-spreading molecule, after years of stable accumulation in plant cells, accelerates redox signalling and affects cellular immunity (32, 37). Elevated levels of cytosolic Ca^{2+} cations increase abruptly the cellular oxidative disorders. Glutathione (GSH) is a major functional low-molecular-weight thiol/protein found in high concentrations in plant cells. GSH is oxidized by ROS as part of the antioxidant protective barrier, participates in the redox signaling, signal transduction cascades (38), and enhanced sensitivity to pathogenesis.

In terms of oxidative disorders, the intracellular levels of ROS concentrations were variable. ROS authorize the plant adaptation and plant cells survival depending on the redox signal intensity and duration (39). Herbal ROS extraction and ROS signaling in plant cells is the presence of the flavonoid B-ring hydroxyl configuration. Flavonoic acids, due to their chelating properties, extract superoxide anions and peroxynitrites, as well as hydroxyl and peroxyl free radical structures (18, 35, 40). Chloroplasts peroxide (H_2O_2) also serves as a redox signal molecule. This redox signal control expression of cytoplasmic ascorbate in the membrane or in apoplasts, possibly after conjunction with secondary ROS (36).

Medicinal plants - antioxidant protective agents against oxidative disorders, radiation-modulating effect, chemoprevention and virus identification

Since several studies, thousands of synthetic anti-cancer chemicals have been described as caused hepatic impairment, followed by acute hepatic symptoms. The ineffective drugs metabolism leaded to liver transplantation cases or death (41, 42). Hepatocytes as primary metabolizing cells in the body carry out detoxification and elimination of xenobiotic and other medicals. Homeostatic dynamic equilibrium of the generation processes and ROS elimination and the prevention of oxidative disorders were also performed in the liver (43).

The efficacy of chemo-preventive plant antioxidants as therapeutic agents against drug-induced toxicity has been proven and widely used in Chinese and Indian traditional medicine. Saad *et al*. (44) reported the pharmacological effects of herbal drugs and plants, used alone or in combinations, which act on synergistic antioxidant mechanisms, thereby neutralized the side effects of cellular ROS and have potential as radioprotectors and cancer therapeutic agents. Plant-derived bioactive compounds provide antioxidant protection against ROS-mediated damages on DNA repair, carcinogen metabolism, scavenging free radicals, inhibition of cellular toxins (10, 45) decreased angiogenesis, and radiation- induced toxicity (46). The mechanism of damages to cellular biomolecules induced by ionizing radiation includes direct and indirect action the latter is mediated via ROS formation. Ionizing radiation has been involved in the metabolic activation of carcinogens, changing intracellular physiology in terms of reductive status and oxidative modification of crucial biomolecules (e.g., DNA, lipid proteins) (47). Therefore, it is not surprising the use of herbal agents and plant extracts mitigates the radiation damage, and also promotes chemo- and virus-prevention.

In the last 2 years in the SARS-COVID-19 pandemic context, herbs and plants are often described as platforms that have been used for the production of reagents and vaccines, particularly through the clinical testing of infectious diseases and VLP-based vaccines. The possible role of herbs and plants against infectious diseases, for the manufacture of small-molecule drugs, recombinant antivirals, subunit vaccines, engineered viruses, and virus-like particle (VLP) vaccines, therapeutic proteins, antibodies, and diagnostic reagents is profitable and will be usable in medical practice (48).

This chapter draws attention to the antioxidant, chemopreventive, radioprotective, and anti-virus properties of medicinal plants and their phytoconstituents.

Silybum marianum

One of the highly appreciated herb, isolated from milk thistle seeds, is Silybum marianum (Silimarin, *S. marianum*) containing a flavonoid complex with active components silibin, silidianin and silicocristine. The beneficial action of *S. marianum* is attributed to the most active ingredient silybin (also called silibinin) (49). As herb with strong antioxidant properties, directly interacting with cell membrane components, *S. marianum* affects inflammatory responses, cytoprotective effects (50), and cellular regeneration in the body. Surai (51) suggested that the antioxidant mechanism of action is due to the stable free-radical scavenging formations and inhibition of enzyme radicals. The treatment with *S. marianum*, in diabetic-burdened patients, leads to the regulation of superoxide dismutase, glutathione peroxidase levels, and total antioxidant capacity (52). Different studies support, the obstruction of metabolic disorders and the stimulatory role of silymarin (53) on insulin resistance and hyperlipidemia.

In vitro experimental data reported that *S. marianum* inhibits lipid peroxidation levels in erythrocyte and hepatocyte cells (54). Bahmani *et al*., (55) reported that silibinin, modulates membrane oxidation of lipids, as well as cell damage in murine hepatocytes. Other evidences of the potent antioxidant effect of *S. marianum* and its active compounds has shown that apart from mediating the FXR-signaling, the herb modulates the nuclear transcription factors (Nrf2; NF-kB) (56). Moreover, the antioxidant protective mechanism of *S. marianum* promotes anti-inflammatory, anti-fibrosis, anti-proliferative effects, and also protects hepatic tissue increase (57-58). The protective potential of *S. marianum* against induced hepatotoxicity and against cancers is probably due to its modulating effect on cells in the early stages of the carcinogenic process. Choi *et al*., (59) found that the *S. marianum* and its active substance silibinin act as therapeutic agents for the treatment of salivary gland cancer by targeting the signaling cascade ERK1/ 2-Bim. *In vivo* studies demonstrate that by inhibiting myeloid-derived suppressor cells in murine models, silymarin suppressed lung cancer growth (60). The hepatoprotective effects of *S. marianum* as a cellular natural antioxidant have clinical applications in chronic and alcoholic liver diseases, liver cirrhosis, mushroom poisoning, diabetic patients and viral hepatitis (61) and prevent glutathione depletion. Ham *et al.,* (62) hypothesized that silibibin could be used as a dietary supplement to treat human placental choriocarcinomas because it inhibits proliferation and induces apoptosis in JAR and JEG3 cells. Recent studies report the role of silymarin and nano-silymarin as cytoprotective agents in normal cells against non-ionizing (UV) or gamma radiation (63-64). Furthermore, the protective role of *S. marianum* in the inhibition of chemically induced carcinogenesis and radiation in colon carcinoma diseases were also established (65).

Studies from 2020- 2021 show that S. marianum, W. somnifera, T. cordifolia, and A. Barbadensis extracts exhibited higher binding energetics than the widely used hydroxychloroquine and other repurposed drugs used for COVID–19 treatment (66). In two other investigations, substances identified in the human metabolome capable of binding the active site of the SARS-CoV-2 main protease (Mpro) (67); a basis for the design of new silibinin-based antiviral therapeutics or supportive care approaches against the SARS-CoV-2 (68). The virus-targeted functions of the flavonolignan silibinin, a potential drug candidate against COVID-19/SARS-CoV, As a direct inhibitor of STAT3—a master checkpoint regulator of inflammatory cytokine signaling and immune response—silibinin might be expected to phenotypically integrate the mechanisms of action of IL-6-targeted monoclonal antibodies and pan-JAK1/2 inhibitors to limit the cytokine storm and T-cell lymphopenia in the clinical setting of severe COVID-19 (69).

Curcuma longa Linn

The active compound of *C. longa*, (turmeric, ginger, Zingiberaceae family) is the lipophilic polyphenol curcumin (stable at acidic pH). Many authors report that curcumin exhibits antioxidant, anti-carcinogenic and anti-inflammatory affects and is mainly metabolised to turmeric glucuronides, sulphates and etc. in the liver (71). Similar to vitamins E and C, curcumin exhibits antioxidant activity leading to the neutralization of the oxidative ischemic heart (72) changes. Curcumin treatment induces autophagy, and prevents vasculature endothelial cells from oxidative stress-related cardiovascular diseases (73). In addition, by exhibiting intracellular antioxidant ability to neutralize oxidative damages, curcumin relieves hepatic oxidative stress in rats with type 1 diabetes (74). New findings highlight, that the use of *C. longa* with identified high levels of basic polyphenol curcumin, improve insulin-mediated lipid accumulation, directly protect fat cells from oxidative disorders and reduced levels of reactive oxygen species (75). It is known that as strong antioxidant *C. longa* similar to silymarin exhibits hepatoprotective effects. Kim *et al*., (75) reported that due to its enhanced hepatoprotective effect, *C. longa* reduced the CCl_4-induced oxidative stress. Simultaneously, leads to increased antioxidant properties by activating the levels of catalase, glutathione S-transferase, glutathione reductase and glutathione peroxidase and reduced glutathione levels. It is proven that low doses of curcumin significantly reduce hepatic impairment caused by chronic alcohol intake and a high fat diet. Probably, antioxidant properties of phenolic groups of curcumin protect cells from lipid peroxidants and modulate the activity of alcohol-metabolizing enzymes and induced hepatotoxicity (72, 76). Several studies underline attenuating effects and the antioxidant role of curcumin, the proliferation of human lymphocytes and the production of inflammatory mediators (72, 77). A similar activity of curcumin was also observed in the propoxur-induced oxidative DNA damage in human peripheral blood mononuclear cells (78). The powerful antidote properties of curcumin are also reported and the ability to neutralize lead-induced genotoxicity, by balancing the activity of the antioxidant protective system in human peripheral blood lymphocytes (79). *C. longa*, with curcumin as the main ingredient, has protective effects against radiation-induced damage, reduces levels of superoxide anion radicals and reduces DNA damage and oxidative stress (72, 80). Rao and co-authors (81), disclose that the use of *C. longa* in the form of mouthwash, had delayed and statistically significantly reduced the levels of radiation-induced oral mucositis, observed in patients undergoing head and neck cancer treatment. Many researchers comment the antioxidant action of herbs and medicinal plant combinations, their high efficacy and lack of residual toxicity in preventing damage from X-ray radiation exposure. In another investigation (46), authors supposed that protective effect of *C. longa* extract against γ-radiation is responsible for modulating the levels of microelements, antioxidant enzymes, and inflammatory cytokines. In addition, *in vitro* protective effect of new RID/ROS natural mixture, containing *C. longa* significantly reduces oxidative stress and DNA double-strand breaks and fully absorbed low doses of X-rays (0.25 Gy) in human umbilical vein endothelial cells (80). Also, *C.longa* extracts stimulate glutathione transferase and prevent cell proliferation possessed breast cancer activity (81).

Haberlea rhodopensis (Friv.)

Typical for the Balkan region *H. rhodopensis* is a perennial medicinal plant, (Gesneriaceae family) rich in luteolin, hexeridine, synapic and ferulic acid, caffeifloylethyanoid glycoside miconoside, characterized by the strong antioxidant properties of its extracts (82). It is proven that the higher phenolic content in 70% ethanol extracts of *H. rhodopensis* directly correlates with high antioxidant activity (82, 83) and increased free-radical inhibition. Georgieva *et al*.,(84) note that *H. rhodopensis* as natural product plays a modulatory role *in vitro* against cellular damage, induced by γ-irradiation and its high antioxidant capacity increases the activity of cellular SOD and CAT. In addition, *H. rhodopensis* extracts after metabolic profiling not reported any cytotoxic activity, have anti-radical properties and are useful as phytotherapeutic agents (85). Kostadinova *et al*., (86) reported that the extracts of *H. rhodopensis* have a beneficial effect on mitochondrial activity, the integrity of cell membranes in human (HaCaT) keratinocytes, by reducing inflammatory processes and reducing ROS. Drought-induced oxidative damages increase the content of polyphenols and two types of glycosides - phenylethanoids and xispidulin 8-C-glucosides in the structure of *H. rhodopensis.* Probably, this plays a protective role on the medicinal plant, helps overcome oxidative changes by reprogramming and redirecting resources to cell protection and significantly increased antioxidant capacity (87, 88). Besides ethanol and methanol extracts of *H. rhodopensis* exhibit an antioxidant effect by reducing H_2O_2-induced toxicity in both normal and malignant cell lines (89). The radioprotective and immunomodulatory properties of the *H. rhodopensis* extract were evaluated in rabbits after 2Gy irradiation (90). The phenolic compounds isolated from H. rhodopensis demonstrate cytoprotective properties and contribute to the inhibition of lipid peroxidation in rat hepatocytes (91).

Tinospora cordifolia (Willd.)

Broad-leaved shrub (*T. cordifolia,* Guduchi, Menispermaceae family) found in tropical parts of India, contains various chemical ingredients such as alkaloids, diterpenoid lactones, steroids, glycosides aliphatic compounds and polysaccharides (92). *T. cordifolia* indicates therapeutic potential in the treatment of asthma inflammatory conditions in a mouse model as modulating the redox signaling (93). Sharma *et al*., (94) noted that extracts inhibit superoxide and hydroxyl radicals, reduce lipid peroxidation, and increase GSH, CAT and SOD levels. The immunomodulatory effects of G1-4A, a polysaccharide derived from T. cordifolia, registered the therapeutic efficacy against tuberculosis *in vitro* and in aerosolized mice models (95). Isolated by *T. cordifolia* compound (1,4)-α-D-glucan (α-D-glucan) activates human lymphocytes and leads to the synthesis of interleukins (IL-6), (IL-18), (IL-1b) and tumor necrosis factors (TNF-α). Cellular bio-regulation leads to reducing the toxicity and genesis of cancerous forms, as well as adapting the processes of proliferation, differentiation, lipid metabolism, and apoptosis (96). The chemoprotective properties of *T. cordifolia* supported the regulation the levels of antioxidant enzymes CAT and SOD, elevation levels of GSH, GPX glutathione S-transferase (GST) and also reduction of lipid peroxidation (97). Additionally, has been reported that the antioxidant properties of *T. cordifolia* increase cytoprotective ability, significantly reduce cellular oxidative disorders and decrease membrane Cd-induced toxicity in Wister rats (98). Therefore, *T. cordifolia* extracts act as a potent hepato- and cardio-protective agent against heavy metal-induced toxicity. Bala and Gupta~~,~~ (99) note that denaturing free radicals compositions of TC extracts support except hepato- but also neoprotective properties against sodium nitrite – induced oxidative stress. Salkar *et al*.,discussed, that *T. cordifolia* reduced SGOT, SGPT, ALP, and bilirubin serum levels and thereby modulates and protects blood and liver at CCl_4-intoxicated animals (100). In another study, herbal extracts of *T. cordifolia* are significantly comparable to doxorubicin cure (100) in cultured HeLa cells**.** Further, Bakrania *et al*., (101) found that the effect of herbal capsules, including seven herbs and medicinal plants, and *T. cordifolia* on DMBA-induced breast carcinogenesis in rats. *Cruel capsule* treatment increases GSH and SOD levels, inhibits tumor progression and increases the chemo-protective effect. In addition, the combined administration of *T. cordifolia* and L-DOPA decreased drug toxicity and protect dopaminergic neurons (102) in Parkinson's disease.

The phytochemicals berberine, β-sitosterol, octacosanol, tetrahydropalmatin, choline from Tinospora cordifolia are potential inhibitors in regulating the function of the 3CLpro protein and provide further control against viral replication and are likely SARS-CoV-19 drugs (103). Natural phytochemicals such as Tinocordiside disrupt the electrostatic interactions between RBD and ACE2 and increase the flexibility of the complex, weakening or blocking the entry of SARSCoV-2 infection (104). Balkrishna et al., 2021 report that the pharmacological effects of aqueous extracts of Tinospora cordifolia (wild.) Hook and Thomson in the form of Giloy Ghanvati tablets (GG) improve pro-inflammatory cell infiltration in the bladder and also save the damage to the tubules and necrosis observed in the kidneys caused by SARS-CoV-2 (105).

Sambucus nigra (Linn.)

The *S. nigra* fruits and flowers have been used in folk medicine to treat various types of diseases. However, their successful use requires further studies on the biological action and the corresponding molecular mechanisms and correlation with its phytochemical composition. *S. nigra* has antioxidant and anti-cancer effects due to its high content of vitamin C and anthocyanins. The registered protective effect in chronic and degenerative diseases is due to the high level of proteins and seven essential amino acids (106).

S. nigra flowers contain higher amounts of chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid, glycosides of quercetin, kaempferol, catechin, ie. possess higher antioxidant and DPPH- scavenging activity compared to fruits (107). *S. nigra* elderberry extracts have immuno-modulating activity in healthy individuals as well as those with viral infections or other diseases characterized by immunosuppression. Some cytokines production activates phagocytes and facilitates their movement to inflammation (108). Two separate studies using monocytes derived from the blood of healthy donors showed that *S. nigra* preparations significantly increased cytokine production (109), and were tested for TNF-α, and IL -1β, IL-6, and IL-8. Lim, 2012 (110) was observed an almost 3-fold increase in IL-10. The most common use of elderberry and elderflower flowers is in the food industry as a food coloring in juices and respectively for flavoring foods. Elderberry fruits, flowers or extracts have great potential for the production of food supplements to be used in phytocompositions. *S. nigra* rutin extracts are a polyphenol bioflavonoid showing a wide range of pharmacological applications due to their significant antioxidant properties. It is commonly used as an antimicrobial, antifungal and antiallergic agent; to treat various chronic diseases such as cancer, diabetes, hypertension and hypercholesterolaemia. The *S. nigra* rutin extracts is preferable to other flavonoids because it is non-toxic, inhibits platelet aggregation, and reduces capillary permeability and *in vitro* anti-inflammatory activity (111-113). Also, Sharma et al., 2013 (113), explain that he *S. nigra* rutin antioxidant properties possessed higher radioprotective effects, in quercetin or hesperidin comparison. The *S. nigra* has ingredients beneficial to the phytocosmetic composition, such as anthocyanins, which can reduce oxidative stress by trapping free radicals, and act as a potential anti-aging agent (114). The active substances in *S. nigra* flowers (115-116) do not decompose under the influence of ultraviolet radiation and show high biological activity. Boroduske et al., 2021, found that *S. nigra* flowers exhibit inhibitory biological activity against the binding of SARS-CoV2 S1 protein receptor domain (RBD) to recombinant human angiotensin-converting enzyme 2(ACE2) receptor *in vitro* based on competitive enzyme-linked immunosorbent assay (117). Moreover, S. nigra polyphenolic extract leads to inhibition of viral replication, dose-dependent viral titers reduction by up to six orders of infection (MOI), respectively infectious process inhibition, and changes of both - viral structures and membrane vesicles (118).

Lemna minor (Linn.)

Lemna minor L. (LME, duckweed, Araceae family) is an aquatic fast-growing, freshwater plant, associated with high toxicological and pharmaceutical capacity (119). The *L. minor* antioxidant effect from the southeastern Bulgarian region is based on 32 biologically active constituents, as: phytosterols (52.8 mg/kg), hydrocarbons (23.1 mg/kg), aldehydes and ketones (20.2 mg/kg), protein (21.80 %), lipids (11.1 mg/kg) (120, 121). *L. minor* is used as an antiscorbutic, depurative diuretic, effective in colds, in the treatment of human diseases such as respiratory tract and tissue inflammations and autoimmune conditions, as an anti-inflammatory antioxidant (122). The high sensitivity, fast growth, and antioxidant enzymatic activities of *L. minor* made it easier to inhibit acute or chronic induced toxicity in an experimental model and were found as an effective antioxidant, with anti-radical possibilities in vitro different assays (123-125). Moreover, *L. minor* maintains a highly efficient ROS scavenging antioxidant defense that limits direct intracellular ROS damages. Also, *L. minor* extract has the potential to scavenge the oxyl and peroxyl radicals, associated with lipid peroxidation, after gamma radiation, and in a bleomycin-induced lung injury model (126- 127).

In the last 5 years, in medicine and pharmaceutical labs were used transgenic plants and modified plant viruses for the development of treatments for human diseases. In particular, *L. minor* was used as a plant host-agro- infiltration agent for Locteron administration (Controlled-release Interferon Alpha 2b), an antiviral treatment for hepatitis C virus infection [128]. Ko et al. 2011, (129) assessed the feasibility of producing a protective antigen for the PEDV spike protein 1 using duckweed, *L. minor*. Stably transformed *L. minor* was obtained by co-cultivation with A. tumefaciens EHA105 harboring the PEDV spike protein gene. The *L. minor* is a potential remediator for the protection of one of the most important aquaculture species in Egypt, the Nile tilapia Oreochromis niloticus, by reducing oxidative stress and enhancing the heavy metal tolerance (130).

CONCLUSION

In modern urbanized life, humans are exposed to increased levels of microorganisms, dietary mutagens, toxins, environmental pollutants, carcinogens, ionizing radiation and viruses. The past 25 years sharply accumulated evidence, supporting the use of natural antioxidants as effective dietary phytochemicals, against ROS/ RNS. Based on the complex nature of medicinal plants, and the role as “redox signaling compounds” they have great potential not only for disease and cancer prevention, but also for improving the recovery by regulating various types of cellular damage caused by radiation, ROS, oxidative stress and virus protection. Plant antioxidants dose protects against oxidative disorders or completely neutralized chemo- or virus- induced oxidative stress. Different studies provide information about efficacy, chemopreventive plant-antioxidants, and microbial species as therapeutic agents against drug-induced toxicity and there were widely used in traditional medicine. Many studies have been performed and are still ongoing to develop a safer and more effective plant- radiao- and chemo- and virus-preventive reagents. Finally, it was indicated in this study that ingredients contained in medicinal plants contribute to self-defense against infectious organisms and to ameliorate oxidative stress.

ACKNOWLEDGMENTS

This study was supported by scientific projects 10/2022, Medical Faculty, Trakia University, Stara Zagora, Bulgaria.

Conflict of interests: No conflict of interests between authors.

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