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Review

Application of nanotechnology to herbal antioxidants as improved phytomedicine: An expanding horizon

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ABSTRACT

Phytotherapy, based on medicinal plants, have excellent potential in managing several diseases. A vital part of the healthcare system is herbal medicines, consisting of therapeutic agents with high safety profile and no or least adverse effects. Herbs or medicinal plants show anticancer, antioxidant, and gene-protective activity, which is useful for pharmaceutical industries. In vitro, the extract of antioxidant compounds prevents the growth of colon and liver cancer cells, followed by a dose-dependent method. The screening of extracts is done by using in vitro models. Reactive oxygen species (ROS) and free radicals lead to diseases based on age which promotes oxidative stress. Different types of ROSs available have central roles in the normal physiology and functioning of processes. Herbal or traditional plant medicines have rich antioxidant activity. Despite the limited literature on the health effect of herbal extract or spices. There are many studies examining the encouraging health effects of single phytochemicals instigating from the medicinal plant. This review provides a detailed overview on herbal antioxidants and how application of nanotechnology can improve its biological activity in managing several major diseases, and having no reported side effects.

1. Introduction

Antioxidants are mainly present in medicinal plants, defined as agents that prevent oxidation chain reactions in different molecules [1]. Herbal plants have a high percentage of phenolic compounds, which acts as antioxidant compounds. Antioxidant compounds have redox properties which show their action by neutralizing the free radicals and decomposing peroxides [2]. Natural antioxidants are considered safe and effective as compared to synthetic antioxidants, which are avoided due to their toxic effect on the body [3]. In the United States, culinary herbs improve the flavor of food products and have been used for many years [4]. Medicinal plants contain various phytochemicals and phenolic compounds [1]. These phytochemicals show antioxidant activity and are used in the treatment of cancer. As a result, there is less mortality in numerous human cohorts [5]. Nowadays, herbal medicines are available as food supplements [6].

Oxidative stress is a significant risk element for health as it leads to severe diseases like diabetes, Alzheimer's disease, cancer, aging, etc. It

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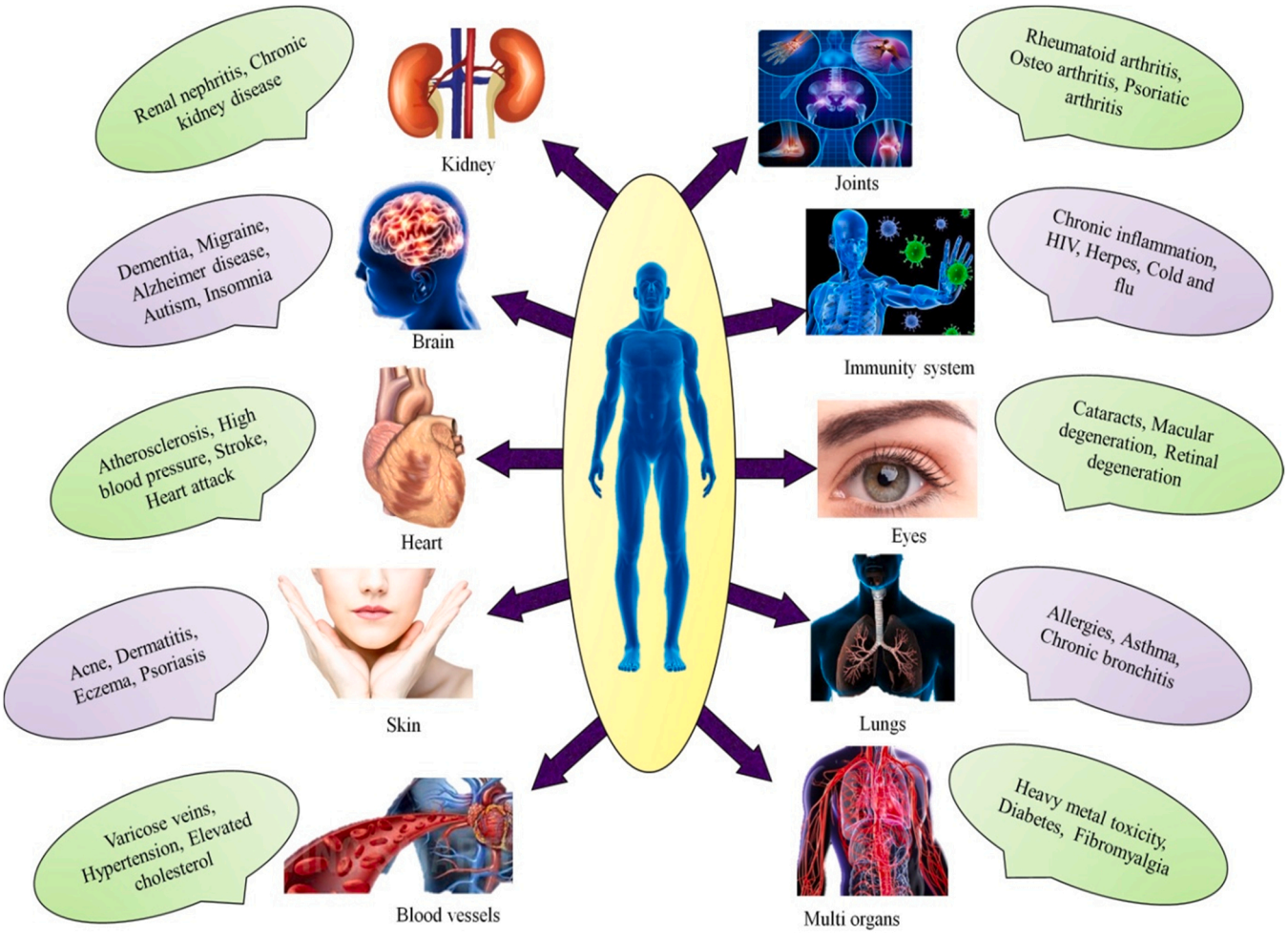


Fig. 1. Effects of reactive oxygen species.

produces Reactive oxygen species (ROS) that disturb the function and structure of the brain′s glial cells resulting in dementia [7]. Herbal antioxidants are proven to be more effective and safer [8]. Phytotherapy has involved herbs and medicinal plants in treating diseases for thousands of years [9,10]. Moreover, the research and scientific publications based on herbal medicines are increasing daily [11]. In biology, the current development regarding free radicals and ROS assures promising results in controlling the diseases [12]. Oxygen is an essential component for the existence of life [13]; however, the destructive effects of oxygen are primarily because of the development of ROS, which can give oxygen to other elements. Free radicals and antioxidants are currently used to treat diseases [12]. Antioxidants are stable molecules that neutralize the electron donated to charged free radicals and reduce the ability to destroy the human body. Antioxidants postpone or stop the damage in human cells due to free radical chain reactions. The antioxidants, having low molecular weight react with free radicals before they lead to damage to the critical molecules. Different antioxidants like uric acid, ubiquinol, and glutathione are produced during normal metabolic rates. The human body has various enzymes that hunt free radicals, consisting of macronutrients, vitamin E, and β-carotene [14,15].

1.1. Search strategy

The systematic qualitative review analyzed globally accepted databases, including peer-reviewed and indexed journals from Scopus, Medline, PubMed, Research Gate, and Google Scholar. Various reports from 2000 to 2022 were included. The search was made using keywords such as herbal antioxidant, Classification of antioxidants, Enzymatic and non-enzymatic antioxidants, Reactive oxygen species, Mechanism of action of antioxidants, Characterization tests for antioxidants, antioxidants in disease management, and nanocarriers containing herbal antioxidants. The botanical names and families of the plants used for herbal antioxidants were mentioned after verification from published literature and databases. Data selection criteria are according to phytoconstituents, in vitro and in vivo models used, nanocarriers, and clinical studies involving herbal antioxidants in disease treatment. The broad inclusion criteria of the reports in the present review are (i) herbal antioxidants reported for various disease treatment, (ii) nanocarriers containing herbal antioxidants used in the management of different diseases, and (iii) herbal antioxidants based clinical trials for various diseases.

1.2. Reactive oxygen species and its effects on normal physiology

The ROS containing oxygen species are reactive and divided into radical and non-radical ROS. Free radical species have unpaired electrons in the outermost orbit, and non-radical species do not contain unpaired electrons. It leads to severe diseases, which affect the whole body, as shown in Fig. 1. However, non-radical ROS are reactive chemically, which get altered to free radical ROS.

1.3. Reactive oxygen species in cell signaling

Cells have to identify their surroundings and transform their activities depending on the microenvironment to survive, which is done by cell signaling. In a simple signal pathway, signals are conveyed by

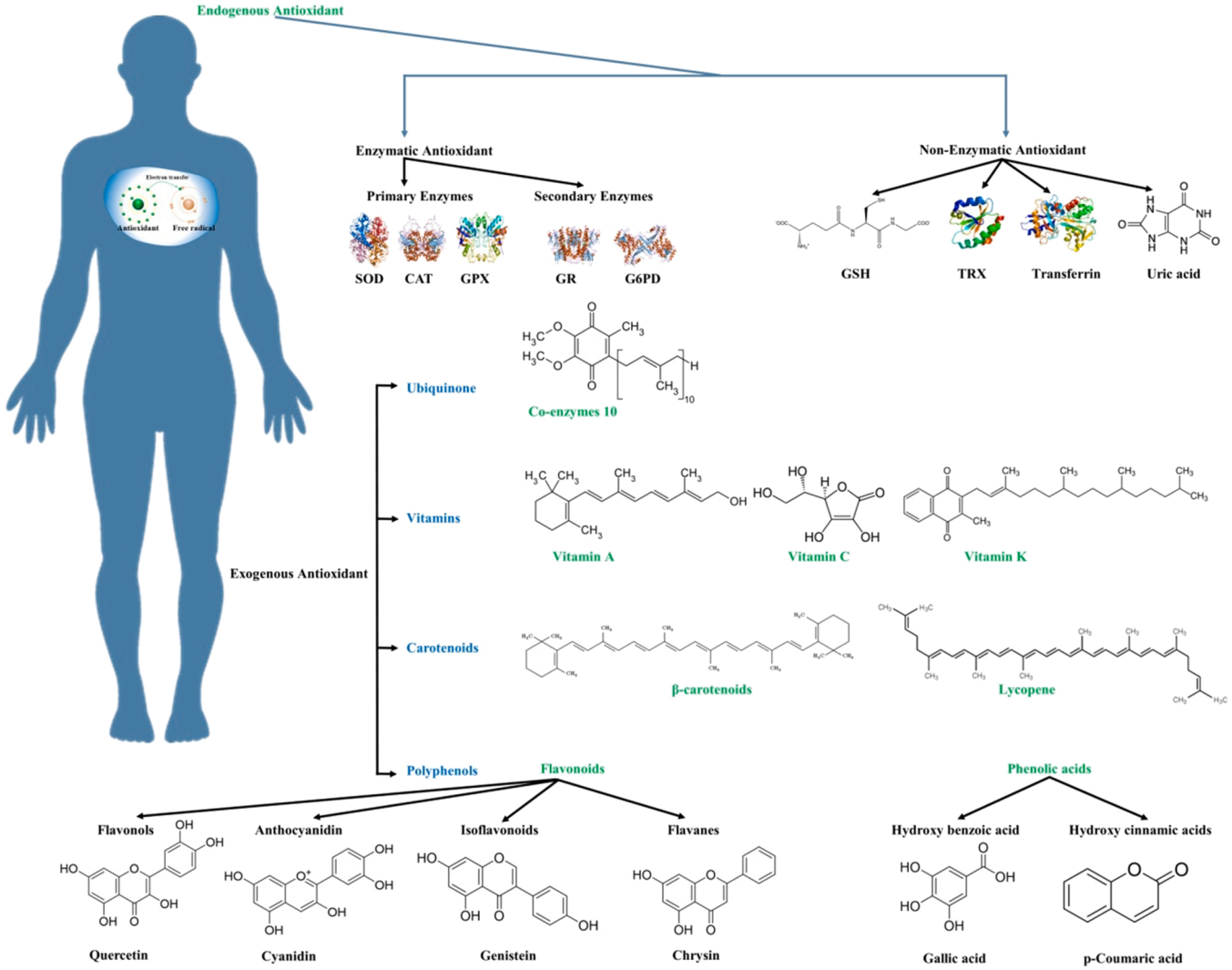


Fig. 2. Types of antioxidants.

modifying the action of proteins. A molecule known as a mediator promotes the step of the signaling pathway, and the purpose of ROS is explained at various places in the signaling pathway. ROS is the prime stimulus that begins the signaling path and the initiator that is the last step of the signaling pathway, also known as effectors [16].

1.4. Formation of reactive oxygen species

The molecules of ROS formed throughout the reduction process of oxygen from water. A single electron addition to oxygen gives superoxide; this reduction process forms hydrogen peroxide (H_2O_2). ROS formation is due to endogenous and exogenous stimuli, which involve ultraviolet (UV) radiation, environmental toxins, and chemotherapy [17]. ROS formation takes place in various cellular sections of enzymes like nicotinamide adenine dinucleotide phosphate (NADPH), nitric oxide (NO), xanthine oxidase (XO), and the electron transport chain of mitochondria [18]. It consists of seven NADPH oxidases, trans-membrane proteins resulting in superoxide or H_2O_2. The additional enzymes are different in their cellular compartment, their ascending activators, and linked subunits. Recognized nicotinamide oxidases inducers are growth elements, vitamin D, and cytokines [19].

Mitochondria are supposed to yield ROS conventionally, simply as an undesirable by-product of energy creation in the electron transmission chain. On the other hand, ROS production also ensues from the mitochondria. This arises at least to some extent by the reluctance of Cytochrome C oxidase using NO brings about more superoxide production deprived of distressing energy creation. Mitochondrial superoxide dismutase (MSOD) alters superoxide into H_2O_2 to pass from the membrane and initiates cytosolic signaling [20].

1.5. How reactive oxygen species are observed?

ROS alters the fabrication, constancy, and role of proteins. Thus redox reaction changes the action of transcription elements in the nucleus. Generally, the reduced transcription factor is connected with deoxyribonucleic acid (DNA) and supports the transcription step. The oxidized transcription factor will not bind to DNA and thus not support transcription. Moreover, the oxidation process of proteasomes exaggerated the protein stability. This oxidation of proteasomes reduces inactive form and does not result in protein degradation [21]. This leads to retaining or high protein levels. Lastly, the role of proteins and molecules could be improved by oxidation from subsequent three approaches:

(1) The proteins, for instance, thioredoxin, are oxidized, causing alteration in protein activity.

(2) This oxidation hunts chaperone protein which generally stops protein action. In oxidation, proteins are separated, commencing their inhibitor, and converted to the active form.
(3) The objectives for oxidation are phosphatases and kinases, which consequently modify the action of proteins by post-translational alterations. Protein tyrosine phosphatases become inactive by oxidation frequently; however various kinases usually become activated. Additional oxidation of targeted molecules can cause permanent oxidative destruction.

Oxidized cysteine residues are the general objective and are secured as oxidation by employing the construction of thiol bridges [22]. The transcription factors consist of activation protein (AP)− 1, nuclear factor erythroid 2–related factor 2 (Nrf2), cyclic adenosine monophosphate response element binding (CREB), Homeobox B5, and nuclear receptors like estrogen receptor [23,24]. Complex antioxidant systems are developed to offset possible lethal ROS effects and allow ROS to perform in the signaling path. It is highly dedicated to relations of both elimination of particular ROS and compartmentalization of antioxidants [18].

2. Classification of antioxidants

The antioxidant enzyme forms an interactive network to prevent cell damage from oxidative stress [25]. During this process, superoxide is released. Firstly, oxidative phosphorylation is converted into hydrogen peroxide (H_2O_2), then reduced to produce water. The multiple enzymes result in a detoxification pathway; the first step involves superoxide dismutase (SOD) catalysis and then various peroxidases removing H_2O_2 [26]. The antioxidants are classified into two types, as shown in Fig. 2.

2.1. Enzymatic antioxidants

2.1.1. Superoxide dismutase

The SODs are antioxidant enzymes; they catalyze the breaking of superoxide anion and give oxygen to H_2O_2 [27]. In all aerobic cells and extracellular fluids, an antioxidant enzyme of SOD is present [28]. Depending upon the cofactor of metal, it consists of three types of most crucial SOD families: Cu^{2+} or Zn^{2+}, Fe^{2+} or Mn^{2+} types, and Ni^{1+} type bind with nickel [29]. As in developed plants, SOD isozymes are confined in several cell compartments. The Mn^{2+} type of SOD is found in mitochondria. The peroxisomes and Fe^{2+} type of SOD are found generally in the chloroplasts. However, antioxidants are identified in peroxisomes. The Cu-Zn type of SOD is confined in peroxisomes, cytosol, chloroplasts, and apoplast [30]. Three different types of SOD exist in humans, i.e., SOD1 (dimer), SOD2, and SOD3 are present in the cytoplasm, mitochondria, and extracellular, respectively. The SOD2 and SOD3 contain four subunits; SOD1 and SOD3 involve Cu and Zn, while SOD2 consist of Mn in their reactive form [31].

2.1.2. Catalase

In most living organisms, catalase enzymes are available for water and oxygen, catalyzing H_2O_2 decomposition [32]·H_2O_2 shows its action as a destructive by-product of various metabolic procedures to avoid damage. It rapidly altered into a reduced amount of harmful substances. The H_2O_2 is decomposed in oxygen and water in cells by the catalase. All the animals utilize catalase in every organ, mainly in the liver in higher concentrations [33].

2.1.3. Glutathione peroxidase

The glutathione system consists of glutathione reductase, peroxidases, and S-transferases. It is present in microorganisms, animals, and plants [34]. The antioxidant enzyme glutathione peroxidase consists of four selenium cofactors. These cofactors catalyze H_2O_2 and organic hydroperoxides. In animals, four different glutathione peroxidase isozymes are present. Glutathione peroxidase 1 works very effectively on H_2O_2. Glutathione peroxidase 4 is more dynamic through lipid hydroperoxides, while glutathione S-transferases indicate more activity about lipid peroxides in the liver. It also shows its function in detoxification [35].

2.2. Non-enzymatic antioxidant

2.2.1. Ascorbic acid

Ascorbic acid is, also known as “vitamin C,” present in both animal and plant sources but not be produced in humans. Therefore, it is essential to consume a diet or have a diet containing vitamin C. It is a vitamin and monosaccharide antioxidant [36]. Animals are capable of synthesizing ascorbic acid in their bodies. Glutathione (GSH) reaction occurs in cells to maintain ascorbic acid in its reduced form. Ascorbic acid is catalyzed using protein disulfide isomerase and glutaredoxins. It acts as an antioxidant, reducing agent, and neutralizes ROS [37]. Ascorbic acid or its substrate plays a vital role in stress management in plants [30].

2.2.2. Glutathione

Glutathione (GSH) is a peptide containing cysteine. It is found in aerobic organisms and produced in cells by amino acids, and is not required in the diet. Glutathione, showing antioxidant activity, consists of a thiol group in its cysteine moiety. It is a reducing agent and reversibly gets oxidized. It is maintained in cells in the reduced form through the enzyme glutathione reductase. As a result, it reduces further metabolites and enzyme systems that react directly with oxidants [38]. Glutathione is a major cellular antioxidant and can be replaced by other thiols [39].

2.2.3. Melatonin

Chemically, antioxidant melatonin is N-acetyl-5-methoxytryptamine [40]. It is a naturally occurring hormone in animals and other living organisms, including algae [41]. Melatonin is an effective antioxidant that easily passes the cell membranes and blood-brain barrier (BBB), which is also a suicidal and terminal antioxidant. Melatonin does not go through redox cycling. Once the melatonin gets oxidized, it is not reduced to its previous state due to numerous stable end-products forming in response to free radicals [42].

2.2.4. Tocopherols and tocotrienols

Vitamin E or Tocopherols and Tocotrienols show antioxidant properties. These are fat-soluble vitamins [43]. Lipid soluble α-tocopherol is the main antioxidant that defends membranes against oxidation by reacting to lipid radicals produced in the lipid peroxidation chain reaction [44,45]. It eliminates the free radical intermediates and protects the propagation reaction by enduring.

2.2.5. Uric acid

Uric acid is a type of non-enzymatic antioxidant, which shows coarsely half capacity of antioxidant in plasma. It facilitates the synthesis of ROS [15,46].

3. Mechanism of action of antioxidants

There are two proposed mechanisms of action for antioxidants: chain-breaking mechanism and ROS/reactive nitrogen species initiators mechanism [47,48]. The mechanism of antioxidants is based on different stages that are defined as follows:

The preventive antioxidants reduce the production of free radicals. While in vivo, the precise mechanism and actual site of radical formation is not explained. The radical-scavenging antioxidant works as the active radical suppressor of chain initiation and propagation reactions. Several endogenous hydrophilic radical-scavenging antioxidants have been identified, while vitamin E is the most effective lipophilic radical-scavenging antioxidant. The de novo antioxidants are based on repairing cells. These recognize, destroy and eradicate increased oxidative

proteins and avoid the building-up of oxidative proteins. Besides, the DNA repair system performs a significant role compared to oxidative damage in the total defense system. Glycosylases and nucleases are enzymes used to repair the injured DNA. Another vital role of antioxidants is adaptation, consisting of production signals and free radical reactions that persuade the development and transportation of suitable antioxidants at a proper place [47].

4. Characterization tests for antioxidants

4.1. DPPH radical scavenging assay

The free radical scavenging capacity of plant extracts can be analyzed using 1, 1-diphenyl-2-picrylhydrazyl (DPPH). To determine the antioxidant activity, a stable DPPH radical is utilized. This assay includes the addition of various extract concentrations in a suitable solvent (10 μL) into 90 μL of methanolic DPPH solution (100 μM) and then a final 100 μL volume in 96 well plates. Then, the ingredients are mixed well and incubated for 30 min at 37 °C. Ascorbic acid is utilized as a standard antioxidant. The microplate reader measures the absorbance at 517 nm compared to the control solution having maximum absorption. This decline in absorbance shows high scavenging activity [49]. The DPPH radical scavenging activity is represented in % form and calculated by:

Inhibition (%) = [(Absorbance of control − Absorbance of test)/ Absorbance of control] × 100.

For evaluation of flavonoids, DPPH radical scavenging activity of quercetin is utilized as standard, and free radical scavenging activity is measured in triplicates [50].

4.2. Ferric-reducing antioxidant power assay

The ferric-reducing antioxidant power (FRAP) assay deals with the reducing ability of antioxidants, which involves reduction in Fe^{3+}-2,4,6-tripyridyl-s-triazine (TPTZ) complex while taking absorbance at 593 nm [51]. The FRAP reagent is prepared by taking acetate buffer 3.6 pH, 10 mmol of TPTZ solution in 40 mmol of hydrochloric acid (HCl), and 20 mmol solution of iron (III) chloride in 10:1:1 (v/v) ratio. Then, 5 μL sample (0.5–2 mg/mL) gets diluted with distilled water (20 μL) and added to the FRAP reagent (150 μL). A microplate spectrophotometer reader measures the absorbance after 8 min at 593 nm. Ascorbic acid is used as standard, and the result is represented in polyphenol-rich extractμmol AA Equivalent/mg [52].

4.3. Oxygen radical absorption capacity assay

Oxygen radical absorption capacity (ORAC) assay evaluates the capability of antioxidants to protect the targeted molecule open to a free radical source. This assay is commonly used to determine oxidative stress and antioxidant by H atom transfer. In this assay, peroxyl radical is mixed with fluorescent probe 3′,6′-dihydroxyspiro[isobenzofuran-1 [3 H],9′[9 H]-xanthen]− 3-one (FL), resulting in a nonfluorescent mixture that easily gets quantitated via fluorescence. The antioxidant inhibits the peroxyl radical-induced oxidation and prevents the deterioration of FL. The antioxidant ability of extract is determined by calculating the reduced rate and quantity of product obtained. The area under the curve (AUC) shows the favorable antioxidant capacity of the antioxidants having a lag phase or without a lag phase. It is beneficial for a wide range of samples, like raw vegetables and fruit, extracts, pure phytochemicals, and plasma. The high-throughput evaluation can regularly examine several hundred samples by one plate-reader combined through a multichannel programmed liquid handling system [53].

4.4. Anti-inflammatory activity

Lipopolysaccharide (LPS) promotes the maturation of dendritic cells, which mainly produce tumor necrosis factor (TNF)-α. In this assay, 100 μg of each flavonoid sample was taken along with salicylic acid and quercetin as standards. For flavonoid derivatives, diene conjugate and conjugated diene assays were performed using a specified method [54]. Flavonoid derivatives were identified by modifying the 96-well microtiter plate method to inhibit hyaluronidase activity [55].

The anti-inflammatory activity of *M. oleifera* flower extract was assessed by the protein denaturation technique using Padmanabhan method. Drug diclofenac sodium acts as a standard non-steroidal anti-inflammatory drug. This standard diclofenac sodium (100 and 200 μg/mL) or 2 mL of *M. oleifera* flower extract (100–500 μg/mL) and 2.8 mL phosphate buffered saline (PBS pH 6.4) was stirred with 2 mL of egg albumin and incubated for 15 min at 27 ± 1 °C. Denaturation was induced by keeping the reaction mixture in the water bath for 10 min at 70 °C. After cooling, the absorbance was measured at 660 nm using double distilled water as blank [56]. The percentage inhibition of protein denaturation was calculated by:

$$\% \text{ inhibition} = A_t\text{-}A_c/A_c x\ 100$$

The LPS convinces dendritic cell growth generating an excessive amount of TNF-α for assessing the antioxidant and anti-inflammatory activity of herbal/plant extracts [57].

4.5. Cytotoxicity assay

The LPS produces pro-inflammatory cytokine in the human monocyte cell line (THP)− 1. In this assay, THP-1 cells were cultured with penicillin and streptomycin (100 U/mL). It was immunized from 10% fetal bovine serum in RPMI 1640 culture media. The cells were separated with phorbol myristate acetate (PMA), and cell plating indicated the test compounds in 0.5% dimethyl sulfoxide (DMSO). The plate should be incubated for 30 min at 37 ℃. The nonlinear regression method is used to calculate 50% inhibitory concentration (IC_{50}) values [58].

4.6. XO inhibitory assay

In XO inhibitory assay, different activities of plant extract were observed spectrophotometrically in aerobic conditions using xanthine as a substrate. The reaction mixture of assay comprised 1 mL extract on various concentrations (0.5–8.0 mg/mL), 0.1 mL solution of XO enzyme (0.1 units/mL of phosphate buffer pH 7.5), and 2.9 mL of fresh phosphate buffer pH 7.5. The reaction started after the pre-incubation for 15 min at 25 ℃ by adding 2 mL of substrate solution containing 150 μM of xanthine in the same buffer. Then the assay mixture was incubated for 30 min at 25 ℃. The addition of 1 mL of 1 N hydrochloric acid stopped the reaction. The absorbance was measured by a spectrophotometer at 290 nm. The allopurinol (0.5–8.0 mg/mL), known as XO inhibitor, was used as per positive controller. AXO unit is enzyme amount essential to yield 1 mmol uric acid/min (25 ℃). The XO inhibitory assay expressed in the form of XO inhibition percent as shown:

$$\text{Inhibition } (\%) = [(A - B) - (C - D)/ (A - B)] \times 100$$

where A is the activity of enzyme deprived of extraction, B is control without enzyme and extraction, and C, D are extraction activities with or without XO, respectively [59].

4.7. Urease inhibitory assay

An improved Berthelot spectrophotometric technique can assess the primary urease inhibitory action of extracts at 625 nm. Inhibition action of hydroxyurea was examined as standard for urease. To prepare the assay solution, 850 μL urea, 0–100 μL extract, and 100 mM phosphate buffer pH 7.4 were mixed. After adding 15 μL urease enzyme, the enzymatic reactions started, which were measured by quantifying

ammonia concentration after 60 min by means of 500 μL solution A, which contained 0.5 g of phenol and sodium nitroprusside (2.5 mg) in 50 mL distilled water and 500 μL solution B, which contained 250 mg of sodium hydroxide and 820 μL of 5% sodium hypochlorite in 50 mL of distilled water for 30 min at 37 °C. The uninhibited urease activity was selected as 100% control activity [60,61].

5. Application of antioxidants in disease management

5.1. Jaundice

Bauhinia malabarica Roxb. belongs to the Leguminosae family, which shows hepatoprotective effect and is used as folkloric medical practice to manage unknown liver diseases. Therefore, the extract of stem bark of *B. malabarica* Roxb. containing methane was tested with the antioxidant markers in liver tissues of Wistar albino rats. The biochemical analysis and the histopathological interpretations of liver expressed hepatoprotective activity of *B. malabarica* Roxb. stem bark [62]. Herbal plants contain phenolic compounds with antioxidant properties reported to treat several diseases like diabetes mellitus, cancer, jaundice, and neurogenerative diseases [63].

Ghaffari, et al. examined multiple doses of methanol active fraction (MAF) and revealed considerably greater levels ($p < 0.05$) of antioxidant enzymes in liver homogenates. The histological study showed the complete neutralization of the carbon tetrachloride (CCl_4)-induced liver injury by the extract. *In vitro* studies proved that the pre-treatment of MAF prohibited the H_2O_2-induced oxidative stress, genotoxicity, and expressively improved (~6-fold, $p < 0.01$) gene expression for the antioxidant enzymes. The *Orthosiphon diffusus* (Benth.) MAF confirmed the hepatoprotective activity contrary to CCl_4-induced hepatotoxicity through antioxidant mechanisms similar to silymarin. The H_2O_2-induced oxidative stress was totally neutralized by MAF from improved gene expression for antioxidant enzymes. Additionally, *Orthosiphon diffusus* MAF is a robust applicant for improving herbal hepatoprotective agents [64]. The various parts, especially flowers and fruits of *Elaeagnus angustifolia* L., have antioxidant properties, which can be used to treat various common illnesses like jaundice, cough, nausea, fever, asthma, and diarrhea [65].

5.2. Alzheimer's disease

Alzheimer's disease (AD) is a prolonged neurodegenerative disease that grows gradually and turns into a significant health-related disease worldwide. Clinically, cognitive declination and progressive dementia are the main features of AD, even though pathologically, amyloid beta (Aß) plaques and tau-neurofibrils are the symbols. Oxidative stress is a major risk factor that results in AD development. ROS can increase the structural and functional abnormalities in the glial cells of the brain resulting in cognitive decline and then dementia. Therefore, antioxidants showed effective results in controlling this oxidative stress in the glial cells. Vitamins A, E, and C show antioxidant action in treating AD [8].

Li et al. investigated that *Spatholobus suberectus* Dunn and *Polygonum multiflorum* Thunb. are very active against DPPH ($IC_{50} = 5.69$, 3.60 μg/mL), butyrylcholinesterase (BChE, $IC_{50} = 4.83$, 5.37 μg/mL), and acetylcholinesterase (AChE, $IC_{50} = 9.11$, 9.27 μg/mL) showing comparative higher TFC (80 and 594 mg RE/g dw), and TPC (267 and 377 mg GAE/g dw), respectively. The authors observed great activity of *Rheum officinale* Baill. extract in FRAP assay (5495.43 μmol Fe^{2+}/g) and 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt assay (ABTS, $IC_{50} = 1.60$ μg/mL). The phytoconstituents obtained by *R. officinale Baill*, *S. suberectus* Dunn, and *P. multiflorum* Thunb. act as important bioactive molecules to treat AD [66].

Ali et al. reported that *Peganum harmala* and *Adhatoda vasica* showed an inhibitory effect on AChE at IC_{50} 68 μg/mL and 294 μg/mL, respectively. Additionally, the potent activity of *F. assafoetida* against COX-1 and the reversible interaction of *A. vasica* against AChE make them effective and promising agents for treating AD [67].

5.3. Hepatic diseases

Several drugs have been used to treat liver damage. However, the remedial effect of acute and chronic liver diseases was frequently not satisfactory. Still, many studies presented that herbal medicines play a vital part in dealing with hepatic disorders due to their potent antioxidant property [68,69]. The extracts of *lobelia* can expressively decrease the stages of glutamic oxalic transaminase (GOT), glutamate-pyruvate transaminase (GPT), and malondialdehyde (MDA), along with the increase in the activity of SOD. This enhanced the free radical scavenging, reduced lipid peroxidation, and stabled cell membrane organization to safeguard the liver from acute liver injury in mice. However, more investigation is necessary to evaluate the pharmacological activity of the constituents and go to clinical trials of liver injury [70].

Ishola et al. reported that Hepacare® containing *Calliandra portoricensis* (Leguminosae), *Canarium schweinfurthii* (Burseraceae), and *Uvaria chamae* (Annonaceae) produced inhibition of DPPH and NO activity depending upon IC_{50} concentration of 48.50 and 55.00 μg/mL, respectively. It suppressed the ABTS(+) absorbance, showing antioxidant capacity (423.47 ± 8.37 mg QUE/g). At the same time, the administered CCl_4 encouraged significant ($P < 0.001$) elevation of 1.70 fold serum aspartate transaminase, 1.60 fold, alanine transaminase, 2.90 fold alkaline phosphatase, and 2.00 fold bilirubin as a contrast to control. This rise in serum biomarkers is dose-dependent inverted by Hepacare® pre-treatment. Furthermore, CCl_4 pre-treatment improved ($P < 0.001$) malondialdehyde (MDA) (73.98%) and reduced ($P < 0.001$) antioxidant enzymes level, however, Hepacare pre-treatment formed dose-dependent reduction of MDA (3.84 fold) having an improvement of glutathione (3.08 fold), superoxide dismutase (2.08 fold) and catalase (3.14 fold) stages in contrast to CCl_4 treated group. Hence, Hepacare is useful in inhibiting CCl_4-induced hepatocellular damage via boosting the endogenous antioxidant systems and scavenging reactive free radicals [71].

5.4. Vitiligo

Flavonoids, glutathione, resveratrol, soybean, and vitamins are the antioxidants in herbal medicines to treat vitiligo. The antioxidant property of plants helps to accelerate the repigmentation of cutaneous in patients suffering from vitiligo [72].

Biological activities related to managing skin diseases are divided into four classes: wound healing, antimicrobial, antioxidant activity, and anti-inflammatory. Drug development and herbal weeds act to treat skin ailments besides encouraging sustainable usage of natural sources [73]. Cinnamaldehyde is the main chemical constituent of *Cinnamomum zeylenicum* Blume consists of two biological activities: an antioxidant effect mediated by Nrf2/ heme oxygenase (HO)− 1 signaling and inhibitory action on aryl hydrocarbon receptor (AHR) activation. Cinnamaldehyde helps to treat disorders allied to oxidative stress like acne, dioxin intoxication, and vitiligo [74].

5.5. Breast cancer

Herbal plants are used to manage cancer globally, as they have ease of availability and effective cost. Different combinations of active constituents existing in plant extract demonstrate synergistic action, increasing the therapeutic activity several folds, recompensing toxicity, and raising bioavailability. The recent work on herbal antioxidants revealed that the butanoic fraction of *Arisaema tortuosum* Wall. tuber demonstrated free radical scavenging action while chloroform and n-hexane fractions of leaves considerably lead to in vitro anticancer perspective in contrast to breast carcinoma (MCF-7) cell. Therefore, it would be the cause of pharmacologically active chemical entities for

revealing novel antioxidants and magic bullets. Still, detailed research is necessary to separate the phytoconstituents and recognize the systematic intracellular pathways responsible for diminishing oxidative stress [75].

Saraca indica L. of Caesalpiniaceae family has therapeutic and pharmacological activities. *S. indica* L. (SIE) extract showed anti-breast cancer and antioxidant activity. By toxicological studies, SIE is proven safe for use and used as a corresponding and substitute treatment for breast cancer treatment [76].

The rhizome of *Cyperus rotundus* L. of Cyperaceae family shows a broad spectrum pharmacological action comprising antioxidant and anti-inflammatory activity. Park et al. investigated that *C. rotundus* L. rhizomes have pro-apoptotic effects in breast carcinoma MDA-MB-231 cell lines. The MDA-MB-231 cells were treated with ethanol and methanol extract but not water extract, resulting in an effective antiproliferative property. Further, the ethanolic extract has more significant action in initiating apoptosis than methanolic extract [77].

5.6. Diabetes

The medicinal plants, herbs, and spices having antioxidant properties deal with the treatment of diabetes [78]. Kalpaamruthaa (KA; comprising an equal ratio of *Semecarpus anacardium* Linn., *Emblica officinalis* Gaertn. and honey) improves the actions of enzymatic antioxidants as well as non-enzymatic antioxidants levels in the pancreas of cardiovascular disorders (CVD)-induced rats. This KA efficiently decreased the carbonyl and lipid peroxides content in the pancreas of CVD-induced rats. It reduced the cellular injury by enhancing the marker enzyme activities in the plasma, liver, and heart. Additionally, KA decreased the CVD by reducing the proteinase activated receptor (PAR)− 1 expression in the heart. Therefore, it plays defending role in type II diabetes by changing PAR-1 [79].

Juneja et al. reported that the hydroalcoholic extract (HAE) of *Callicarpa arborea* Roxb. stem bark contained hypoglycemic property ($p < 0.05$), showing antidiabetic action as compared to the normal control experimental rats group. HAE proved as safe and effective in doses up to 2000 mg/kg body weight of rat. Hence, the HAE of *C. arborea* Roxb. stem bark acts like herbal antioxidants to prevent and treat oxidative stress-induced diabetes mellitus. The presence of flavonoid and phenolic contents is accountable for the antidiabetic effect of *C. arborea Roxb.* stem bark [80].

Tiong et al. investigated the in vitro antidiabetic and antioxidant activity of various alkaloids of *Catharanthus roseus* (L.) leave extract. Four alkaloids, such as vindoline I, vindolidine II, vindolicine III, and vindolinine IV, were determined and isolated from dichloromethane extract (DE) of leaves. The DE and isolated compounds were not cytotoxic in pancreatic β-TC6 cells at the maximum dose of 25 μg/mL. These four alkaloids convinced more glucose acceptance in pancreatic β-TC6 or the myoblast C2C12 cells, including vindolicine III expressing maximum activity. Furthermore, the II-IV compounds revealed noble protein tyrosine phosphatase-1B inhibition action. Alkaloid vindolicine III indicated the maximum antioxidant ability in DPPH and ORAC assays. It reduced the H_2O_2-induced oxidative injury in β-TC6 cells at 12.5 μg/mL and 25 μg/mL concentrations [81].

5.7. Psychiatric disorders

Psychiatric disorders include insomnia, anxiety, stress, seizures, and epilepsy [82]. These disorders, specifically neurodegenerative diseases, are due to oxidative and free radical induced stress [83]. The antioxidant property of medicinal plants is one of the widely used approaches. The reduction of ROS and oxidative stress helps in the prevention of disease. *Ginkgo biloba* L. containing ginkgolides showed antioxidant and neuroprotective, including cholinomimetic activities. The efficiency of ginkgolides and Ginkgo extract in Alzheimer's disease has been found to be comparable to prescribed drugs like donepezil or tacrine. More significantly, Gingko does not show side effects. Various other plants like *Melissa officinalis* and *Salvia officinalis* have antioxidant, cholinergic, and memory-improving activities [84].

Phytoflavonoids show various valuable ameliorative properties on altered neurological illnesses by their antioxidant effect. Singh et al. investigated the effect of flavonoid-rich ethyl acetate fraction of crude fig (*Ficus religiosa* L.) extract combined with phenytoin on seizure harshness, depressing behavior, and intellectual shortage in pentylenetetrazol (PTZ)-kindled mice. The extract demonstrated the important antioxidant properties in different in vitro free radical scavenging assays. The combined administration of fraction (2.5, 5, and 10 mg/kg; i.p.) and sub-effective dosage of phenytoin (15 mg/kg; i.p.) in post kindled animals once a day till 15 days presented a dose-dependent reduction in the severity of seizure score, fewer mistakes, more step-down potential in passive shock evasion model, and declined rigidity period in tail suspension experiment as in contrast with only phenytoin-treated group. The biochemical studies of tissue brain presented amelioration of reduced catalase and acetylcholinesterase (AChE) activities, reduced GSH levels, and thiobarbituric acid reactive substances (TBARS) by oxidative stress destruction. Authors found that flavonoid-rich fraction of *F. Religiosa* L. has a defensive effect besides phenytoin sub-effective amount in cognitive shortage linked to PTZ-kindling and the depressing behavior include the oxidative stress reduction. It associates the requisite clinical assessment of flavonoid supplementation laterally through antiepileptic drugs (AEDs) to treat epilepsy, psychiatric and cognitive disorders [85].

6. Nanotechnology enabled nanocarriers containing herbal antioxidant

The fastest growing and most exciting research field is the development of colloidal nanoparticles (NPs). It shows a compelling impact on the development of nanotechnology over the past decades. The fabrication of nanoparticles through herbal extracts plays a vital role in nanotechnology. It is called green technology because it does not involve harsh chemicals. The central goal of green methods is to utilize harmless biomolecules like carbohydrates, DNA, enzymes, proteins, and plant extracts to produce biocompatible NPs; however, these biomolecules are somewhat costly, simply decomposable, and can be adulterated.

The *Salvia miltiorrhiza* Bunge (Danshen) stimulates blood circulation and represents worthy antioxidant action. Liu et al. demonstrated that formulations prepared by nanotechnology showed greater antioxidant bioactivities than the antioxidant properties of herbal plant-based formulations fabricated by traditional grinding techniques. Their results showed that active constituents in nanotechnology trials unconstrained faster as associated with samples powdered traditionally [86].

6.1. Metal nanoparticles

Silver (Ag) and gold (Au) NPs are two generally synthesized plasmonic NPs showing their unique inherent activities. AgNPs are active and worldwide accepted germicidal agents to several microbes. The preparation of AgNPs from plant extracts offers modest, one-step, and fast processes compared to other production methods. The extracts produced from different plant parts show their action as possible reducing and stabilizing agents used to produce AgNPs of different sizes and shapes. The extraction method employed differs based on the variety of content present in the extracts. The usage of plant extracts yields many advantages compared to other biomolecules (peptides, proteins, enzymes, and DNA). These are cheap, easily producible, and available. These are environmentally approachable NPs with the capability for large-scale production. Plant extract-directed NPs are used in many bioanalytical and biomedical uses as antioxidants, antimicrobial agents, diagnostic tools, anticancer agents, therapeutics, and drug delivery agents [87].

Table 1
Structures and biological sources of phytoconstituents explored as prophylactic and therapeutic agents in the treatment of various diseases.

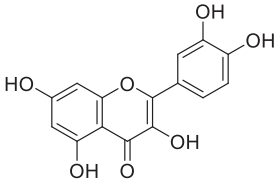
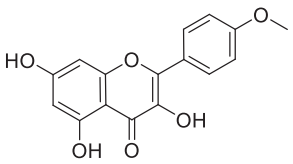
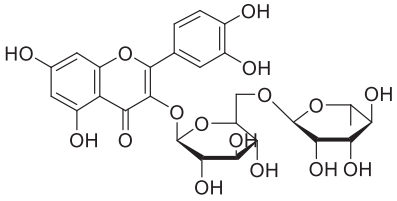
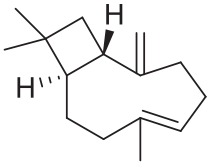
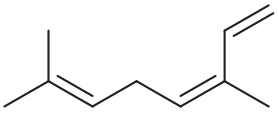
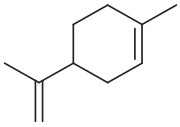
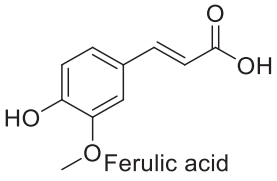
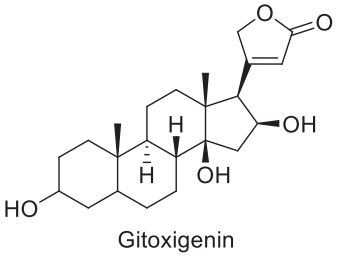
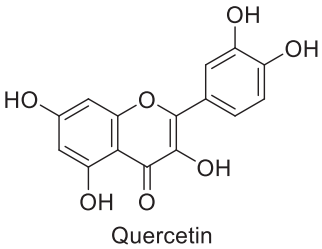
Biological source	Family	Active constituent (s)	Pharmacological activities	References
Bauhinia malabarica Roxb.	Leguminosae	 Quercetin  Kaempferol  Rutin	Hepatoprotective	[62]
Orthosiphon diffusus (Benth.)	Lamiaceae	 Caryophyllene  ß-ocimene  Limonene	Hepatoprotective	[64]
Elaeagnus angustifolia L.	Elaeagnaceae	 Ferulic acid  Gitoxigenin  Quercetin	Hepatoprotective	[100]

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Table 1 (*continued*)

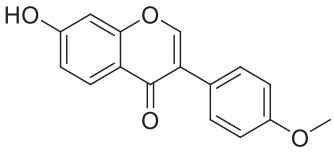
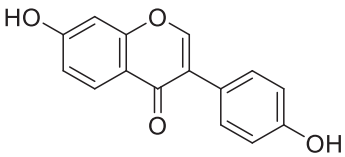
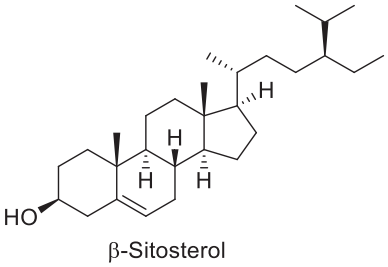
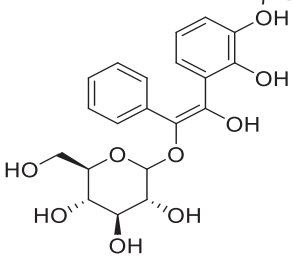
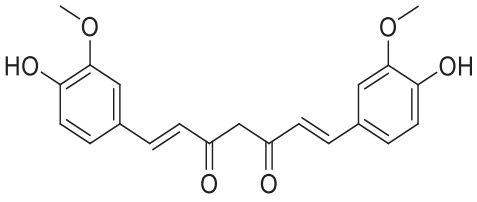
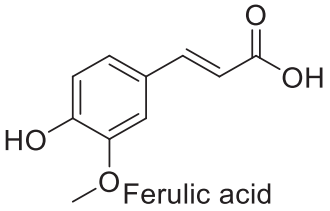
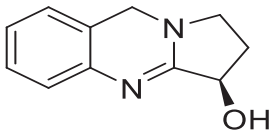
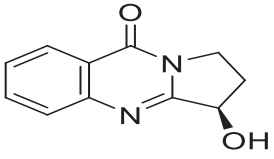
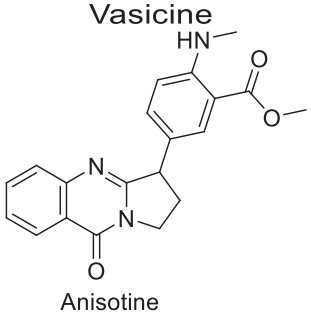
Biological source	Family	Active constituent (s)	Pharmacological activities	References
Spatholobus suberectus Dunn	Leguminosae	 Formononetin  Daidzein  β-Sitosterol	Alzheimer's disease, Renal clearance	[66,101]
Polygonum multiflorum Thunb.	Polygonaceae	 Tetrahydroxy stilbene	Alzheimer's disease	[66]
Rheum officinale Baill.	Polygonaceae	 Curcumin	Alzheimer's disease	[66]
Ferula assafoetida L.	Umbelliferae	 Ferulic acid	Alzheimer's disease	[67,102]
Adhatoda vasica Nees	Acanthaceae	 Vasicine  Vasicinone	Alzheimer's disease, Oligospermia	[67,103]
Calliandra portoricensis (Jacq.) Benth	*Leguminosae*	 Anisotine	Hepatoprotective	[67,104]

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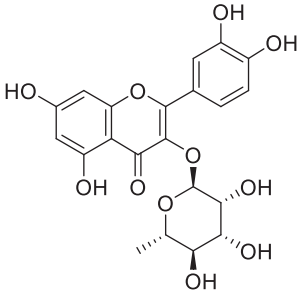
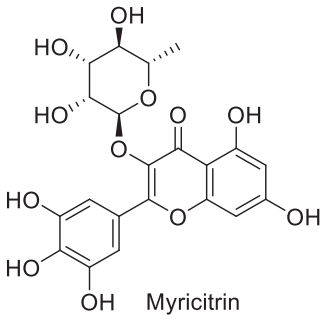
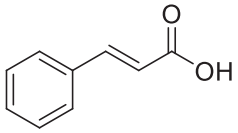
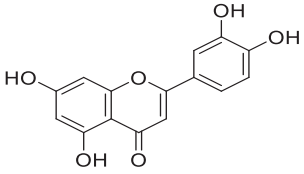
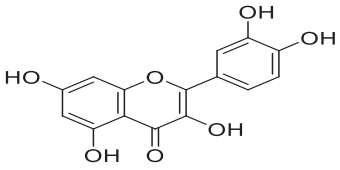
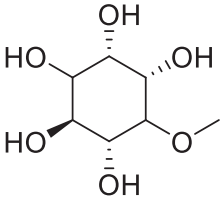
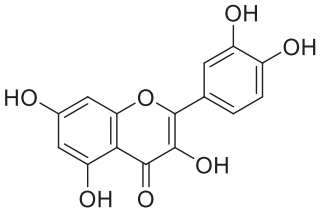
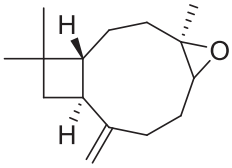
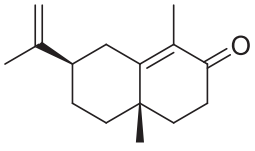
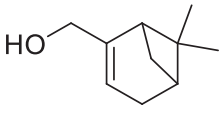
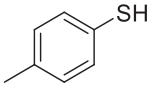
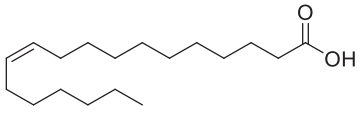
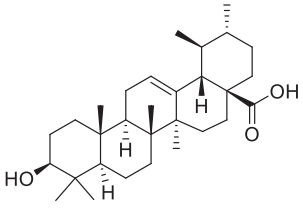
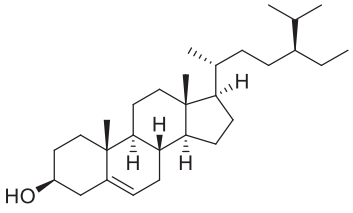
Table 1 (*continued*)

Biological source	Family	Active constituent (s)	Pharmacological activities	References
Cinnamomum zeylanicum Blume	Lauraceae	 Quercitrin  Myricitrin	Vitiligo	[74]
Arisaema tortuosum (Wall.) Schott	Araceae	 Cinnamaldehyde	Breast cancer	[75]
Saraca indica L.	Caesalpiniaceae	 Luteolin  Quercetin	Cancer	[76,105]
Cyperus rotundus L.	Cyperaceae	 Pinitol  Quercetin	Cancer	[77,106]
Semecarpus anacardium Linn.	Anacardiaceae	 Caryophyllene oxide  α-Cyperone  Myrtenol	Diabetes	[79]
Callicarpa arborea Roxb.	Lamiaceae	 p-Thiocresol  cis-Vaccenic acid	Diabetes	[80]
Emblica officinalis Gaertn.	Euphorbiaceae	 Ursolic acid  β-Sitosterol	Cardiovascular disorders	[79]

(*continued on next page*)

Table 1 (*continued*)

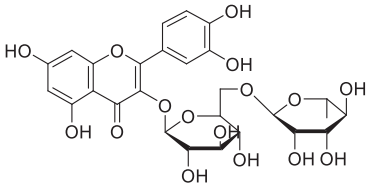
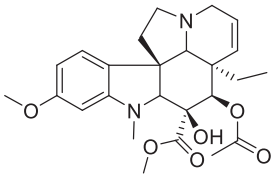
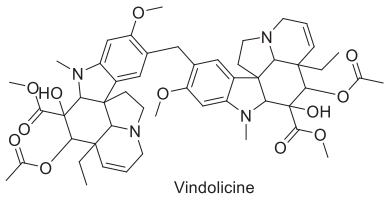
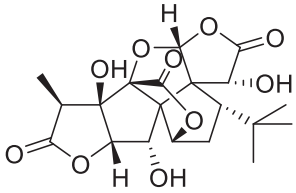
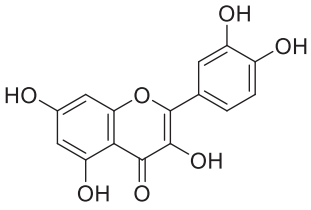
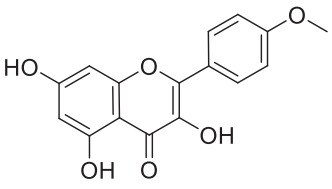
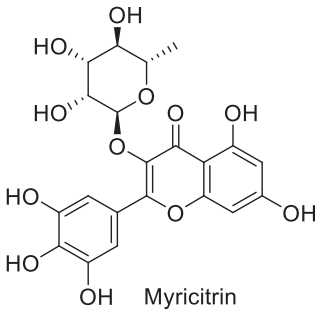
Biological source	Family	Active constituent (s)	Pharmacological activities	References
Catharanthus roseus (L.) G.Don	Apocynaceae	 Rutin	Diabetes	[81]
Ginkgo biloba L.	Ginkgoaceae	 Vindoline  Vindolicine	Psychiatric disorders	[84,107]
Ficus religiosa L.	Moraceae	 Ginkgolide	Psychiatric disorders	[85]
Melissa officinalis L.	Lamiaceae	 Quercetin  Kaempferol  Myricitrin	Psychiatric disorders	[84,108]

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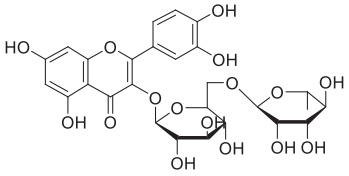
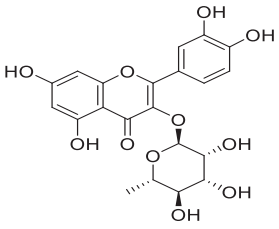
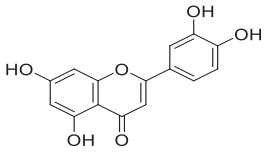
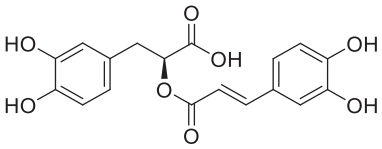
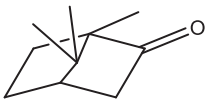
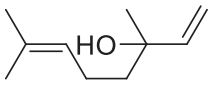
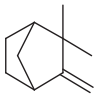
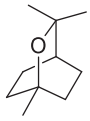
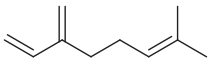
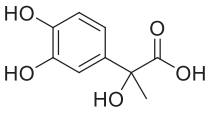
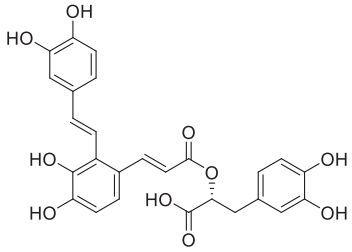
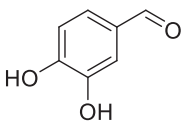
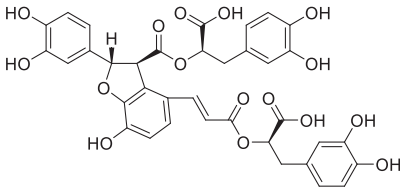
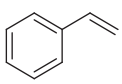
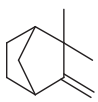
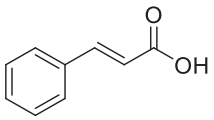
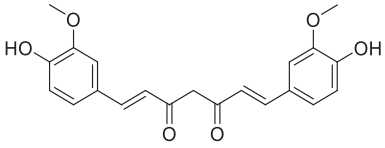
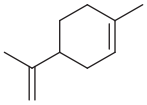
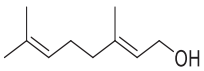
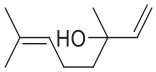
Table 1 (*continued*)

Biological source	Family	Active constituent (s)	Pharmacological activities	References
Salvia officinalis L.	Lamiaceae	 Rutin  Quercitrin  Luteolin	Psychiatric disorders	[84,109]
Salvia miltiorrhiza Bunge	Lamiaceae	 Rosmarinic acid	Hypertension	[87,110]
Cinnamomum cassia (L.) J.Presl	Lauraceae	 Camphor  Linalool  Camphene  1,8-Cineole  Myrcene  Danshensu  Salvianolic acid A  Protocatechuic aldehyde  Salvianolic acid B	Anti-oxidant	[88,111]
Curcuma longa L.	Zingiberaceae	 Styrene  Camphene  Cinnamaldehyde	Cancer and infectious disease	[92]

(*continued on next page*)

Table 1 (*continued*)

Biological source	Family	Active constituent (s)	Pharmacological activities	References
Coriandrum sativum L.	Apiaceae	 Curcumin  Camphor  Limonene  Geraniol  Linalool	Anti-oxidant	[97,112]

Shakeel et al. worked to determine the protective action of *Cinnamomum cassia* (L.) bark-based titanium dioxide NPs (TiO_2NPs) administered in rats. Subcutaneous injection of 150 mg/kg bodyweight of TiO_2NPs or TiO_2 bulk salt along with the cinnamon extract indicated ameliorative properties of the antioxidant system, protecting characteristic histological injuries and certain hematological limits in the rat liver cured with TiO_2NPs or bulk salt [88].

Nagaich et al. developed AgNPs by flavonoids of apple extract and incorporated them into hydrogels. The synthesized AgNPs were evaluated by UV spectroscopy, zeta potential, surface morphology, and particle size. AgNPs loaded hydrogels were tested for viscosity, physical appearance, spreadability, antioxidant studies by DPPH radical scavenging assay, pH, porosity, *ex vivo* permeation, in vitro release, and antibacterial activity on *E. coli* and *S. aureus*. Hydrogels showed 98.01 ± 0.37% in vitro release and 98.81 ± 0.24% *ex vivo* permeation in 24 h. The percent radical inhibition value was found to be 75.16 ± 0.04%, proving its great antioxidant property [89].

Barbinta-Patrascu et al. used a simple and eco-friendly bottom-up method to fabricate silver bio-nanostructures by *Salvia officinalis* L (sage) leaf extract. The sage showed bioreduction properties during AgNPs preparation, which was evaluated by UV–VIS and ATR-FTIR spectroscopy. To increase biocompatibility and stability, sage AgNPs were hosted in two liposomes, i.e., Chla-DPPC- and soybean lecithin-lipid vesicles. X-Ray Fluorescence study proved the presence of silver in liposomes or sage-AgNPs biohybrids. Herbal AgNPs or liposomes bioconstructs stability was determined by zeta potential magnitude. Chla-DPPC or sage-AgNPs was a more stable biohybrid with a value of zeta potential − 34.2 mV. Antioxidant activity evaluation of silver bio-nanostructure was done by chemiluminescence assay. These advanced environmentally friendly silver phytonanostructures developed by saga extract marked robust 86.5–98.6% antioxidant activities [90].

6.2. Polymeric nanoparticles

The p-hydroxybenzyl alcohol (HBA), a herbal agent containing phenolic compounds, protects from diseases related to oxidation damage. Park et al. established a novel biodegradable peroxalate copolymer wherein HBA was incorporated chemically in its backbone. This HBA-incorporated copolyoxalate (HPOX) was prepared by the condensation reaction of oxayl chloride and 1,4-cyclohexamethanol. It released active HBA by hydrolytic degradation. It was also dispersed in a single emulsion meant to prepare NPs of 500 nm diameter. The HBA NPs prevent the formation of nitric oxidase, which suppresses the inducible nitric oxide synthase (iNOS) in lipopolysaccharide (LPS)-activated RAW 264.7 macrophage cells. Moreover, HPOX NPs reduced the TNF-α production. The outstanding property of HPOX is the complete degradation of the polymer [91].

Using pH and heating-induced electrostatic adsorption techniques, the pectin coating was magnificently employed on NaCas/zein NPs. The pectin coating has not distressed the particle size and polydispersity index (PDI) of NaCas/zein NPs. Moreover, it intensely amended their physical strength in simulated gastrointestinal situations. Curcumin, an active constituent of *Curcuma longa* L., containing NaCas/zein NPs coated with pectin 490 boosted its antioxidant property in an aqueous medium and delivered controlled release in simulated gastric and intestinal fluids on oral delivery [92].

Novel rutin-loaded zein-sodium caseinate NPs were synthesized by using their antioxidant activity. The quantity ratio of zein for sodium caseinate, ethanol, and rutin expressively affect the physical features of zein NPs. The rutin-loaded NPs were found to be round with high encapsulation efficacy. The DPPH and ABTS assays showed 52.7% and 71.2% free radical scavenging activity. The total antioxidant capacity was found to be 0.40 nmol/g. Based on these results, zein-sodium caseinate NPs can be employed as a novel nano carrier system for rutin and other water insoluble active ingredients [93].

6.3. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are encouraging colloidal delivery systems, which help to deliver the herbal compounds to different organs, comprising the brain, through oral delivery. The extent of drug present in phytocompounds encumbered in SLNs was found to be around 5–10 times more than its native type. In addition, the controlled release of the bioactive compounds of herbs through oral delivery can be attained by surface alteration of the SLNs. This unlocks the path for improving different new phytocompounds loaded in SLNs to manage various chronic ailments [94].

6.4. Herbal Kudingcha nanoparticle

The Kudingcha NPs are spherical, having a size of 100–600 nm. The acute toxic effects proved that it is a harmless constituent. The Kudingcha NPs were more significant in dropping the body weight, adipose tissue, and fatty liver paralleled to plain Kudingcha. It is a powerful lipid-lowering agent that plays an essential part in managing hyperlipidemia and disease related to the fatty liver [95].

Table 2
Clinical studies highlight the application of phytochemicals in the treatment of various diseases [113].

Clinical trial ID	Study Title	Disease	Phase	Study start/ completion date	Type of formulation	Intervention	Summary
(A) Completed							
NCT02634216	Effects of Capros in patients with type-1 diabetes (CarposT1D)	Type 1 diabetes	Not applicable	January 2015/ May 2016	–	Dietary supplement: Capros, 250 mg, twice a day	The effect of gooseberry *Phyllanthus emblica* on blood glycemic index in patients with Type 1 diabetes was attributed to the presence of polyphenols.
NCT02920125	Study the result of Ayurvedic SUVED & REIMMUGEN (colostrum) treatment on vascular disease, CAD, CVA, DVT (SHARP)	Coronary artery disease (CAD), Cerebrovascular disease (CVD), Ischemic heart disease, Deep vein thrombosis (DVT), peripheral arterial diseases, vascular disease	III	January 2016/ September 2017	Capsule	Drug: SUVED comprising of many herbs including *Emblica officinalis* or combination product: REIMMUGEN or: grain flour placebo; 500 mg, once a day for 3 months	The reduction and/or reversal of symptoms and clinical progress in vascular disease, Coronary artery disease, and stroke were observed.
NCT02866539	Effect of polyherbal compound for control of blood sugar in impaired glucose tolerance and diabetes	Diabetes mellitus	Not applicable	December 2016/ December 2017	Capsule	Drug: Polyherbal capsule coccinia, bougainvillea, catharanthus	Blood glucose levels were lowered after treatment with the polyherbal formulation.
NCT03143803	Control of blood glucose fluctuation with the usage of polyherbal	Diabetes mellitus	Not applicable	May 2017/ April 2017	Capsule	Drug: Polyherbal capsule coccinia, bougainvillea, catharanthus, once a day for 14 days	The estimation of glycemic control using polyherb indicated its potential in treating diabetes.
NCT05258123	*Ginkgo biloba* extract in the treatment of schizophrenia	Schizophrenia	Not applicable	May 2017/ June 2018	–	Drug: *Ginkgo biloba* extract (360 mg) or placebo tablets for 12 weeks	Down-streaming of symptoms and improvement of cognitive learning.
NCT01524380	*Ginkgo biloba* extract for schizophrenia	Schizophrenia	Not applicable	September 2011/ June 2013		Drug: *Ginkgo biloba* extract (Egb761), 400 mg/day, twice a day, 10 weeks or Placebo	Add-on therapy as a combination of Egb761 and risperidone (2–6 mg) may potentiate the therapeutic effects of risperidone in treating schizophrenia.
NCT01046292	Effect of *Ginkgo biloba* special extract LI 1370 on dual-tasking in patients with MCI	Mild cognitive impairment	IV	January 2010/ February 2015	Capsule	Drug: *Ginkgo biloba* (120 mg GBE) once a day or placebo	The change in gait speed and cognitive learning may be improved with GBE.
NCT03790033	Efficacy and safety of Ucha-Shinki-Hwan on Korean patients with cold hypersensitivity in the hands and feet-double blinded, randomized, multicenter, placebo-controlled clinical trial	Cold hypersensitivity	II and III	December 2018/ September 2019	Granule	Drug: Ucha-Shinki-Hwan (consist of Rehmannia root 1.7 g, Achyranthes root 1.0 g, Cornus fruit 1.0 g, Dioscorea rhizome 1.0 g, Psyllium husk 1.0 g, Alisma rhizome 1.0 g, Hoelen 1.0 g, Moutan root bark 1.0 g, Cinnamon bark 0.3 g, Pulvis Aconiti Tuberis Purificatum 0.3 g: 2.5 g three times a day	The herbal formulation may improve sensitivity towards cold and hot and prevent itching.
NCT00010803	*Ginkgo biloba* prevention trial in older individuals	Dementia, Alzheimer's disease	III	October 2000/ April 2008	–	Drug: *Ginkgo biloba* (Egb 761), 120 mg twice a day	Memory improvement was observed with Egb, i.e., 0.043 than placebo 0.041 and executive functions 0.092 from 0.089. No mortality was reported; however, minor side effects such as bleeding (8.93%) and stroke (5.18%).
NCT00672373	Extract of *Ginkgo biloba* and tardive dyskinesia	Tardive dyskinesia, schizophrenia	III	December 2006/ May 2007	Capsule	Drug: Extract of *Ginkgo biloba* (EGb-761, 80 mg each capsule), 3 capsules each day for 12 weeks or placebo	Synergistic effect of Egb761 on lowering of tardive dyskinesia associated with antipsychotic drugs.
NCT02181972	Efficacy and safety of *Ginkgo biloba* in middle-aged cognitively intact adults	Cognitive learning	III	May 2002/ November 2002	Tablet	Drug: *Gingko biloba* or placebo	The efficacy and safety of *Gingko biloba* film-coated tablets in improving cognitive

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Table 2 (*continued*)

Clinical trial ID	Study Title	Disease	Phase	Study start/ completion date	Type of formulation	Intervention	Summary
							learning in middle-aged persons were evaluated.
NCT00446485	Efficacy and safety of *Ginkgo biloba* extract in mild cognitive impairment and cerebrovascular insufficiency	Mild cognitive impairment, cerebrovascular insufficiency	IV	May 207/ April 2010	Tablet	*Ginkgo biloba* standardized extract 24/ 6 tablets, 120 mg/day (60 mg two times daily) during 6 months or placebo	Improvement in mild cognitive learning was observed after treatment with *Ginkgo biloba* extract.
NCT00276380	A Study on the use of Tanakan for recovery of neurological impairment following ischemic stroke	Stroke, acute neurological impairment	III	February 2003/ March 2009	Tablet	Drug: EGb761, 40 mg tablets (2 tablets, 3 times a day, 240 mg/day for 6 months or placebo	Egb761 regulated neurological improvement and showed mortality in a few patients (4.95%) with minor side effects such as cardiac failure, atrial fibrillation, and cellulitis.
NCT02321475	EGb 761 (Tanakan) effectiveness in the treatment of patients of middle age and younger with psycho-emotional symptoms, added to cognitive disorders	Cognitive disorders	–	June 2014/ April 2015	–	Drug: EGb761	The effectiveness of treatment in patients with cognitive disorders was estimated.
NCT01160692	A study to evaluate The effects of a multivitamin/ mineral with Ginko in subjects with age associated memory impairment	Age-related memory disorders	III	February 2006/ July 2008	Tablet	Dietary supplement: Multivitamin/ multimineral/ Ginkgo (BAY 81–2775) daily oral intake of film-coated tablets for 3 months or placebo	The safety and efficacy of Ginkgo tablets were estimated in the aged population.
NCT02982603	Efficacy and safety of qinggongshoutao bolus in amnestic mild cognitive impairment	Mild cognitive impairment herbal medicine allergy	IV	May 2015/ December 2017	Pills	Drug: Qinggongshoutao bolus or Ginkgo biloba extract 761 or placebo, 2 pills per time, twice a day for 48 weeks.	Improvement in memory ability was estimated.
NCT00276510	A study of EGb 761 (Tanakan) in dementia of alzheimer Type onset in patients suffering from memory complaints	Memory disorders, age-related retention disorders, cognitive	IV	February 2002/ November 2009	Tablet	Drug: EGb 761 (Tanakan) 120 mg, 1 tablet twice a day, oral route, during 5 years or placebo	Efficacy and tolerance of Egb761 were determined in patients with cognitive disorders.
NCT01201187	Efficacy and safety study of combination of Ginkgo extract and Ginseng extract (YY-162) in children with Attention deficit hyperactivity disorder (ADHD)	Mental disorders	III	March 2010/ April 2010	Tablet	Drug: YY-162, Ginkgo extract 30 mg + Ginseng extract 50 mg) 1Tablet/ twice a day for 8weeks, po medication or placebo	The synergistic effects of Ginkgo and Ginseng on treating mental disorders were investigated.
NCT01536210	Efficacy and safety study of combination of Ginkgo extract and Ginseng extract in children with Attention deficit hyperactivity disorder (ADHD)	Mental disorders	III	December 2011/ August 2012	Tablet	Drug: YY-162, Ginkgo extract 30 mg + Ginseng extract 50 mg) 1tablet/ 3 times a day for 8 weeks, PO or placebo	Combination effects of Ginkgo and Ginseng on brain disorders were determined.
NCT00814346	Effect of EGb761 on brain glucose metabolism in three groups of elderly defined by cognitive functions	Alzheimer's disease, cognitive impairment	II	March 2016/ February 2019		Drug: EGb761, four weeks for Alzheimer's disease patients, 18 months for MC and CNE patients or placebo	The lower value of cognitive tests-clock drawing test score in MC and CNE Groups (−3 to 2) than placebo (−5 to 3) and better test score in cognitive tests-age-adjusted logical memory (1) indicated efficiency of treatment. No deaths were observed after treatment with Ginkgo, however ischemic attacks occurred in 4.35% patients. Few also reported non-serious side effects such as vomiting, diarrhea, and fatigue.

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Table 2 (*continued*)

Clinical trial ID	Study Title	Disease	Phase	Study start/ completion date	Type of formulation	Intervention	Summary
NCT00164749	A pilot study of curcumin and Ginkgo for treating Alzheimer's disease	Alzheimer's disease	I and II	October 2004/ July 2006	Capsule, Powder	Drug: Placebo and Ginkgo extract, placebo once daily, 120 mg/day standardized ginkgo leaf extract or curcumin and ginkgo extract; 1 g/4 g curcumin once daily, capsules/ powder and 120 mg/day standardized ginkgo leaf extract	Combination effects of curcumin and Ginkgo in alleviating Alzheimer's disease were determined.
NCT00010920	Preventing cognitive decline with alternative therapies	Dementia, memory disorders	III	September 1999/ December 2004	–	Drug: *Ginkgo biloba* extract	Treatment with *Ginkgo biloba* extract may prevent dementia, thus may be used to enhance memory sustainability.
NCT01672359	Evaluating whole foods supplementation on cognition	Sub-optimal cognitive function, sub-optimal immune function	NA	May 2011/ December 2011		Dietary supplement: Ginkgo synergy and Choline (120 mg/day *Ginkgo biloba* leaf with 80 mg/day with 40 mg/ day grape seed extract) and choline (700 mg choline/ day) or OPC synergy and catalyn (00 mg/day of grape seed extract with 50 mg/day green tea extract (60% catechins)) and vitamins) or placebo	Impairment of memory and immune functions were estimated with combination of Ginkgo, grape extract and choline.
NCT00042172	Treatment for early memory loss	Cognition disorders, Alzheimer's disease	IV	June 2002/ September 2004	–	Drug: Donepezil or *Ginkgo biloba* extract	The efficacy of donepezil will be potentiated by co-administration of Ginkgo extract.
NCT03228550	Omega-3 fatty acids and exercise on mobility and cognition in older women	Aging, cognitive decline	II	February. 2017/ December 2018	–	Dietary supplement: Efamol active 50 (1000 mg docosahexaenoic acid, 160 mg eicosapentaenoic acid, 20 μg B12, 1 mg folic acid, 124 mg phosphatidylserine, 240 mg *Ginkgo biloba* extract and 20 mg vitamin E) or placebo	The synergistic effects of omega fatty acid, vitamins and herbals in treating memory loss in aged women were investigated.
NCT01009476	Long-term use of galantamine versus nootropics (memory enhancing drugs) in patients with Alzheimer's dementia under conditions of daily routine	Dementia, Alzheimer's disease, Alzheimer's dementia	–	March 2006/ August 2008	Capsule	Drug: Galantamine i.e. galantamine (8 mg,16 mg, 24 mg retard capsule) or nootropics (*Ginkgo biloba*, nicergoline piracetam, or others)	Effects of galanamine and nootropics in cognitive disorders were estimated.
NCT03482063	The effects of 12 weeks supplementation with a B-vitamin and herbal supplement on neurocognitive function and mood	Neurocognitive function Mood	II	June 2018/ January 2020	Tablet	Dietary supplement: Swisse ultiboost memory + focus (made up of brahmi, Ginkgo, vitamin B12 and B3), 2 tablets daily or placebo	Effect of combination supplement in neurodegenerative disorders was estimated.
NCT03382067	Influence of chocolate with plant additives on episodic memory in healthy subjects experiencing test anxiety	Test anxiety	NA	December 2017/ August 2018	–	Dietary supplement: High epicatechin/ melissa (comprises of 2.8 g acticoa chocolate + 7.2 g caster sugar + 5 g melissa), once a day	Alleviation of anxiety after treatment with polyherbs was investigated.
NCT00110552	Effects of sage on memory and mental performance in Alzheimer's disease patients	Alzheimer's disease	I	July 2005/ October 2014	Capsule	Drug: *Salvia officinalis* (sage)	The efficiency of cognitive enhancer on memory and cognitive performance was estimated.
NCT01033630	Cardiovascular-protective effects of herbal medicine danshen-gegen	Hypertension	II	January 2006/ May 2008	Capsule	Drug: D&G 2 g or 1 g (contains Danshen: *Salvia miltiorrhiza* Bge and	The adjuvant therapy may act as cardio protective agent.

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Table 2 (*continued*)

Clinical trial ID	Study Title	Disease	Phase	Study start/ completion date	Type of formulation	Intervention	Summary
						Genen: *Pueraria lobata* (willd.)) or placebo	
NCT05210218	Cinnamon and withania on weight loss	Obesity	NA	January 2018/ June 2019	Capsule	Dietary supplement: *Cinnamomum cassia* and *Withania somnifera* (300 mg + 150 mg, respectively) or placebo	The reduction in obesity after treatment with Cinnamon and Withania was estimated.
NCT03778099	The effect of cinnamon on ovulation induction in women with polycystic ovary syndrome	Polycystic ovary syndrome (PCOS) Ovulation	III	September 2018/ February 2020	Capsule	Drug: Cinnamon Capsule 500 mg, 2 capsules twice a day, for 3 months or placebo	The efficiency of Cinnamon on ovulation induction with Polycystic ovary syndrome (PCOS) in women was estimated.
NCT03388762	RCT of a polyherbal dietary supplement for prediabetes	Prediabetic state	Not applicable	December 2017/ January 2020	Tablet	Dietary supplement: Glucosupreme herbal tablet contains mixture of constituents including cinnamon bark or placebo	Glycemic control in prediabetic patients on treating with polyherbal formulation was determined.
NCT03290417	Correlative analysis of the genomics of vitamin D and omega-3 fatty acid Intake in prostate cancer	Prostate cancer	Not applicable	September 2017/ December 2019	Capsule	Dietary supplement: Vitamin D (5000IU) 1 capsule daily or omega-3 (720 mg) capsule, 3 capsules daily or turmeric (250 mg), 2 capsules, 4 times daily	The slow rate of growth of prostate cancer in men was monitored.
NCT01859858	Effect of curcumin on dose limiting toxicity and pharmacokinetics of irinotecan in patients with solid tumors	Advanced colorectal cancer	I	June 2013/ October. 2016	–	Dietary supplement: Curcumin or irinotecan	Beneficial effects of turmeric against dose limiting toxicity and biofate of irinotecan.
NCT01917890	Radiosensitizing and radioprotectve effects of curcumin in prostate cancer	Prostate cancer, radiation therapy	Not applicable	March 2011/ October 2013	Capsule	Dietary supplement: 74 Gt radiation exposure followed by curcumin 6 capsules of 500 mg each or placebo	Synergistic effects of radiation therapy and co-administration of curcumin.
NCT01160302	Curcumin biomarker trial in head and neck cancer	Head and neck cancer	I	June 2010/ January 2016	–	Drug: Microgranular curcumin C3 complex, 4 g twice a day for 21–28 days	Protective effects of curcumin in alleviating head and neck cancer
NCT01333917	Curcumin biomarkers	Colorectal cancer	I	November 2010/ January 2013	Tablet	Drug: Curcumin C3 tablet (4 g), daily for 30 days	Reduction in burden of colorectal cancer by use of curcumin.
NCT01042938	Curcumin for the prevention of radiation-induced dermatitis in breast cancer patients	Breast cancer	II	January 2008/ April 2011	Capsule	Drug: Curcumin C3 complex capsule (500 mg), 4 times a day for 4–7 weeks by orally or placebo	The reduction in dermatitis (2.6), pain intensity (1.14) was observed after treatment with curcumin. Also, no mortality, serious and non-serious adverse effects were reported.
NCT03211104	Comparison of duration of treatment interruption with or without curcumin during the off treatment periods in patients with prostate cancer undergoing intermittent androgen deprivation therapy	Prostate cancer	Not applicable	August 2007/ August 2015	Capsule	Dietary supplement: Curcumin	The efficiency of curcumin influenced duration of treatment of prostate cancer undergoing androgen deprivation therapy.
NCT03482401	Disposition of dietary polyphenols and methylxanthines in mammary tissues from breast cancer patients	Breast cancer	Not applicable	June 2017/ December 2019	Capsule	Dietary supplement: Polyphenol capsules (containing lemon, orange, pomegranate, olive, grape, cocoa, curcuma and broccoli extracts), 3 times a day	The study helped to predict rate of deposition of polyphenol and methylxanthines in mammary tissue.
NCT01201694	Phase I study of surface-controlled water soluble curcumin (Theracurmin)	Advanced Cancers	I	October 2011/ January 2014	Capsule	Drug: Surface-controlled water soluble curcumin, 100 mg twice a day for 28 days	The investigation helped to estimate maximum tolerable dose of curcumin.
NCT03063320	The effect of spice consumption on	Cardiovascular risk factor	Not applicable	January 2017/	–	Other: Spice blend (includes: cardamom,	The effect of regular consumption of spice on

(*continued on next page*)

Table 2 (*continued*)

Clinical trial ID	Study Title	Disease	Phase	Study start/ completion date	Type of formulation	Intervention	Summary
	postprandial vascular function			December 2018		coriander, cumin, ginger, paprika, red pepper, turmeric, cinnamon) at three different doses (0.6 g, 3.7 g and 7.4 g) respectively for 4 weeks	postprandial vascular function was estimated.
NCT02599272	Effects of mixed spices on cardiometabolic function - the polyspice (PSP) study	Cardiometabolic risk	Not applicable	October 2015/ March 2018	–	Other: Rice with tomatoes/ vegetables and peeled aubergine (no spice) with o without spice	The study investigated efficiency of spices rich in polyphenol in improving postprandial cardiac functions.
NCT03064958	The acute effect of spices on vascular health	Oxidative stress	Not applicable	September 2016/ March 2018	–	Other: Herbs and spices with fat rich diet	The level of oxidative stress markers were evaluated in patients on high fat diet and co-administration of spices.
Ongoing clinical trials							
NCT03633630	Efficacy and safety study of DCB-AD1 in patients with mild to moderate Alzheimer's disease	Dementia, Alzheimer's disease	II	September 2005/ Not given	–	Drug: DCB-AD1, a herbal formulation of root of Fo-ti (*Polygonum multiflorum),* once a day for 24 weeks	–
NCT03633630	Amla on metabolic syndrome, insulin sensitivity and insulin secretion	Metabolic syndrome	I and II	August 2019/ Ongoing	Capsule	Drug: Amla capsule 500 mg twice a day for 90 days or placebo	–
NCT04801745	Vegan diet, amla fruits and uric acid	Hyperuricemia diet, healthy cardiometabolic syndrome	Not applicable	March 2021/ Ongoing	Capsule	Drug: Amla fruit or healthy diet, double controlled placebo for 3 months or 1 year	–
NCT03479983	Effect of Indian gooseberry extract (AMX160) in hypercholesterolemia	Hypercholesterolemia	IV	June 2018/ August 2019	Capsule	Dietary supplement: AMX160; 500 mg *Phyllanthus emblica* L. fresh fruit extract capsules, twice a day for 90 days	–
NCT05182788	The efficacy evaluation of choleswise pressed candy on cardiovascular health	Cardiovascular diseases	Not applicable	Active, not recruiting	Candy	Dietary supplement: Cholewise pressed candy, 2 tablets per days for 8 weeks	–
NCT04874961	Olive polyphenols in cardiovascular prevention	Metabolic syndrome, high blood pressure, high cholesterol, dyslipidemias, high blood sugar	IV	Recruiting	Capsule	Dietary supplement: Tensiofytol or combination cholesfytol; 67.2 mg red yeast rice powder (*Monascus purpureus*; equivalent to 2.9 mg monacoline K) 1000 mg amla dry extract (*Phyllanthus emblica*)	–
NCT03090516	Clinical efficacy of *Ginkgo biloba* extract in the treatment of Alzheimer's disease	AD	II and III	August 2016/ March 2020`	Tablet	Drug: *Ginkgo biloba* dispersible tablets 0.15 g at a time , three times a day.	–
NCT03980509	A window trial on curcumin for invasive breast cancer primary tumors	Breast cancer	I	January 2020/ June 2022	–	Drug: Curcumin 500 mg, twice a day, Oral	–
NCT04121728	Modulation of attention in event related potential (ERPs) as a marker of early cognitive decline by *Ginkgo biloba* (AgilGinkgo)	Subjective cognitive decline cognitive performance functional capacity age-related cognitive decline	Not applicable	September 2019/ March 2020	–	Drug: *Ginkgo biloba* extract or placebo at a rate of 2 capsules of 120 mg per day for 170 days.	–
NCT04492241	Ginkgo leaf extract and *Armillariella mellea* powder oral solution for the treatment of motoric cognitive risk syndrome	Motoric cognitive risk syndrome, mild cognitive impairment, Aging locomotive syndrome	Not applicable	July 2021/ Ongoing	Powder	Drug: Ginkgo leaf extract and *Armillariella mellea* powder oral solution or simulation of Ginkgo leaf extract and *Armillariella mellea* powder oral solution	–
NCT01294072	Study investigating the ability of plant exosomes to deliver curcumin to	Colon Cancer	I	January 2011/ Ongoing	Tablet	Dietary supplement: Curcumin or its plant exosomes, 3.6 g daily for 7 days	–

(*continued on next page*)

Table 2 (*continued*)

Clinical trial ID	Study Title	Disease	Phase	Study start/ completion date	Type of formulation	Intervention	Summary
	normal and colon cancer tissue						
NCT04266275	Topical curcumin for HPV related cervical disease	Neoplasm cervix	II	March 2022/ December 2022	Capsule	Drug: Curcumin C3 complex capsule (500 mg), 4 capsules a day	–
NCT02782949	Curcumin in preventing gastric cancer in patients with chronic atrophic gastritis or gastric intestinal –metaplasia	Chronic atrophic gastritis	II	April 2017/ Ongoing	–	Drug: Curcumin, orally	–
NCT05045443	Safety and efficacy of curcumin in children with acute lymphoblastic leukemia	Acute lymphoblastic leukemia, pediatric	II	August 2021/ Ongoing	Capsule	Drug: Curcumin capsule (500 mg), twice daily, orally	–
Studies withdrawn/terminated/unknown status							
NCT00070954	*Ginkgo biloba* to improve short-term memory losses associated with electro convulsive therapy (ECT)	Memory, short-term	I and II	February 2003/ January 2005	–	Drug: *Ginkgo biloba* or placebo	–
NCT01637168	Comparison of the *Panax ginseng* + associations to *Ginkgo biloba* in the treatment of cognitive function disorders	Memory deficit	III	Not provided/ Withdrawn		Drug: *Panax ginseng* + *Ginkgo biloba* + Polyminerals + Multivitamin or *Ginkgo biloba* (Tebonin)	–
NCT00500500	Effect of EGb 761 on patients with mild to moderate Alzheimer's disease	Alzheimer's disease	II	January 2005/ Terminated	–	Drug: EGb 761 (Tanakan) or placebo	–
NCT03647384	Guilingji capsule for mild-to-moderate cognitive impairment	Cognitive dysfunction	II	August 2018/ December 2019	Tablet	Drug: Gulingji capsules or *Ginko biloba* extract tablet	–
NCT01416818	Treatment of depression in Parkinson's Disease	Depression in Parkinson's Disease	II	May 2008/ December 2011	Pill	Drug: Xiaoyao Pill or Bupleurum + Ginkgo, two times a day for 12 weeks without dose changing or placebo	–
NCT01825759	Danshen dropping pill for coronary heart disease heart and artery structure and function	Cardiovascular heart disorders (CHD), Hypertension	IV	January 2013/ December 2014	Pill	Drug: Danshen dripping pill, 27 mg ten pills by mouth every 8 h for one year	–
NCT01563770	Cardiovascular effects of *Salvia miltiorrhiza* extract (Danshen)	Dyslipidemias, hypertension, vasodilation, oxidative stress inflammation	Not applicable	April 2012/ March 2013	Capsule	Dietary Supplement: *Salvia miltiorrhiza* extract or placebo; 1.5 g twice daily for four consecutive weeks	–
NCT01637675	Efficacy and safety study of sodium tanshinone IIA sulfonate on pulmonary hypertension	Pulmonary hypertension, pulmonary arterial hypertension, cardiovascular diseases, lung diseases	III	May 2013/ December 2014	–	Drug: 20 mg sildenafil citrate by mouth or sodium tanshinone IIA sulfonate (active constituent *Salvia miltiorrhiza*) of diluted with 5% glucose solution, 20 mg sildenafil citrate, oral	–
NCT03610412	*Cinnamomum cassia* effect on IGF1 and metabolic control in patients with Diabetes mellitus 2 without glycemic control metformin treated	Diabetes mellitus	II	August 2019/ December 2020	–	Dietray supplement: *Cinnamomum cassia*	–
NCT00479973	The anti-diabetic and cholesterol-lowering effects of Cinnamon and cassia bark	Type 2 Diabetes mellitus, Hyper cholesterolemia	II	September 2007/ May 2008	–	Dietary Supplement: Cinnamon force which is mixture of *Cinnamomum aromaticum* and *Cinnamomum verum* or placebo	–
NCT03593837	Efficacy and safety of HQGZWWT patients with rheumatoid arthritis	Rheumatoid arthritis	II and III	October 2018/ March 2020	Granules	Drug: Huang qi gui zhi wu wu granule or placebo	–
NCT02488252	Semi-individualized Chinese medicine treatment as an adjuvant	Diabetic nephropathies	II	July 2015/ September 2021	–	Drug: Semi-individualized Chinese Medicine treatment	–

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Table 2 (*continued*)

Clinical trial ID	Study Title	Disease	Phase	Study start/ completion date	Type of formulation	Intervention	Summary
	management for diabetic nephropathy						
NCT04294836	Curcumin in advanced cervical cancer	Cervical cancer	II	December 2021/ Ongoing	Tablet	Drug: Curcumin or placebo	–
NCT02554344	Effect of curcumin in treatment of squamous cervical intraepithelial neoplasias (CINs)	Cervical intraepithelial neoplasia	I	March 2016/ January 2017	–	Drug: Curcumin 500 mg, orally, 2 times a day for 12 weeks	–
NCT00295035	Phase III trial of gemcitabine, curcumin and celebrex in patients with metastatic colon cancer	Colon neoplasm	III	March 2006/ March 2007		Drug: Celecoxib or curcumin	–
NCT00486460	Phase III trial of gemcitabine, curcumin and celebrex in patients with advance or inoperable pancreatic cancer	Pancreatic cancer	III	June 2005/ Not given		–	Drug: Gemcitabin or curcumin or celebrex
NCT03847623	Effect of preoperative curcumin in breast cancer patients	Breast cancer	Not applicable	June 2018/ December 2020	Capsule	Dietary Supplement: Curcumin or placebo, twice a day	–
NCT02321293	A open-label prospective cohort trial of curcumin plus tyrosine kinase inhibitors (TKI) for EGFR -mutant advanced NSCLC	Lung cancer	I	August 2015/ December 2016	–	Dietary supplement: Curcuviva (curcumin); 80 mg per oral daily for 8 weeks or tyrosine kinase -inhibitor gefitinib; 250 mg per oral daily	–
NCT02724202	Curcumin in combination with 5-Fluorouracil for colon cancer	Metastatic colon cancer	I	March 2016/ June 2020	Capsule	Drug: Curcumin in form of soft gelatin capsule containing 500 mg of pure curcuminoid or 5-Fluorouracil	–
NCT02944578	Topical curcumin for precancer cervical lesions	Neoplasms	II	November 2017/ Suspended	Capsule	Drug: Curcumin (500 mg), 4 capsules a day for 12 weeks	–
NCT01948661	Anthocyanin extract and phospholipid curcumin in colorectal adenoma	Colorectal adenoma	Not applicable	March 2014/ December 2019	–	Dietary Supplement: Mirtoselect (cyanidin-3-glucoside) + Meriva (curcumin)	–
NCT00969085	Trial of curcumin in cutaneous T-cell lymphoma patients	Cutaneous T-cell lymphoma	II	November 2012/ November 2014		Drug: Turmeric, 2 sticks (8 g) per day for up to 6 months or placebo	–

6.5. Carbon dots

The carbon dots (CDs) presented tremendous fluorescence intensity (in blue, red, and green filters), great photo-stability, and effectual multi-colored fluorescent emission depending on the excitation. The non-aqueous solvable curcumin is altered to extremely hydrophilic CDs. The passivation of the surface results in improving the rate and extent of drug and fluorescent activities. The passivated carbon dots (CDP) are spherical with a size below 10 nm. CDP is simple, economical, and effective. Depending on the cellular application and excitation, CDP showed outstanding multi-fluorescent properties, optical behaviors, and surface functionalization [96].

Sachdev and Gopinath worked on the green fabrication of CDs by leaves of *Coriander sativum* L. and represented their ability as a sensor, antioxidant, and bioimaging agent. Authors treated coriander leaves hydrothermally to prepare CDs and investigated their antioxidant properties [97].

6.6. Dendrimers

The combination of dendrimers with herbal antioxidants reveals the advancement of the drug delivery system (DDS) for cancer management. The use of dendrimers in nanomedicine helps to reduce the inherent toxic effects of anticancer agents. Therefore, it enhances the treatment efficacy and patient compliance [98]. The Chimeric advanced drug delivery nano systems (chi-aDDnSs) are defined as combined nanosystems with various biomaterials that have great potential as DDS. Alkannin and shikonin are hydroxyl naphthoquinones that occur naturally and have a fixed spectrum of antimicrobial, wound healing, antioxidant, anti-inflammatory, and currently recognized antitumor action. Kontogiannopoulos et al. worked on the three generations of hyperbranched aliphatic polyesters to form complexes using shikonin and liposomal Chi-aDDnSs. The authors observed drug encapsulation, drug release profile, and examined the physical stability of Chi-aDDnSs at 4 °C. Their results are encouraging and may be utilized to design in vivo experiments [99].

The structures of different phytoconstituents explored as prophylactic and therapeutic agents in the treatment of various diseases have been represented in Table 1.

6.7. Clinical trials

Clinical trial data have depicted the role of different herbs in the treatment of various pathological conditions. The details of completed,

ongoing, and withdrawn clinical trials investigating the potential of herbals in treating a plethora of diseases are presented in Table 2.

7. Conclusion

Phytotherapy is safe and effective therapy based on traditional medicine. Anticancer drugs lead to nephrotoxicity by initiating oxidative stress, damage-associated molecular patterns (DAMPs) production, inflammatory processes, and cell apoptosis, whereas herbal plants and their products acts as to decrease the nephrotoxicity and side effects of anticancer drugs via their antioxidant and anti-inflammatory properties. Herbs or herbal medicines comprise the significant antioxidant property. More research is required to study the effects of antioxidant-rich herbs and spices based on oxidative-stress ailments.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] S.C. Lourenço, M. Moldão-Martins, V.D. Alves, Antioxidants of natural plant origins: from sources to food industry applications, Molecules 24 (2019) 4132, https://doi.org/10.3390/molecules24224132.

[2] F. Mraihi, M. Journi, J.K. Chérif, M. Sokmen, A. Sokmen, M. Trabelsi-Ayadi, Phenolic contents and antioxidant potential of Crataegus fruits grown in Tunisia as determined by DPPH, FRAP, and β-carotene/linoleic acid assay, J. Chem. 2013 (2013) 1–6, https://doi.org/10.1155/2013/378264.

[3] B. Nisar, A. Sultan, S. Rubab, Comparison of medicinally important natural products versus synthetic drugs-a short commentary, Nat. Prod. Chem. Res. 6 (2018) 1–3, https://doi.org/10.4172/2329-6836.1000308.

[4] E.I. Opara, M. Chohan, Culinary herbs and spices: their bioactive properties, the contribution of polyphenols and the challenges in deducing their true health benefits, Int. J. Mol. Sci. 15 (2014) 19183–19202, https://doi.org/10.3390/ijms151019183.

[5] W. Zheng, S.Y. Wang, Antioxidant activity and phenolic compounds in selected herbs, J. Agric. Food Chem. 49 (2001) 5165–5170, https://doi.org/10.1021/jf010697n.

[6] E. Ernst, Herbal medicine in the treatment of rheumatic diseases, Rheum. Dis. Clin. N. Am. 37 (2011) 95–102, https://doi.org/10.1016/j.rdc.2010.11.004.

[7] R. Harvey, M. Skelton-Robinson, M. Rossor, The prevalence and causes of dementia in people under the age of 65 years, J. Neurol. Neurosurg. Psychiatry 74 (2003) 1206–1209, https://doi.org/10.1136/jnnp.74.9.1206.

[8] V. Mehta, N. Desai, A. Perwez, D. Nemade, S. Dawoodi, S.B. Zaman, A.C. E. Alzheimer's, The role of vitamin A, C and E (ACE) in oxidative stress induced Alzheimer's disease, e000086-e000086, J. Med. Res. Innov. 2 (2018), https://doi.org/10.15419/jmri.86.

[9] W. Kooti, M. Farokhipour, Z. Asadzadeh, D. Ashtary-Larky, M. Asadi-Samani, The role of medicinal plants in the treatment of diabetes: a systematic review, Electron. Physician 8 (2016) 1832–1842, https://doi.org/10.19082/1832.

[10] A. Ota, N.P. Ulrih, An overview of herbal products and secondary metabolites used for management of type two diabetes, Front. Pharmacol. 8 (2017) 436, https://doi.org/10.3389/fphar.2017.00436.

[11] O. Tabatabaei-Malazy, A. Ramezani, R. Atlasi, B. Larijani, M. Abdollahi, Scientometric study of academic publications on antioxidative herbal medicines in type 2 diabetes mellitus, J. Diabetes Metab. Disord. 15 (2016) 1–8, https://doi.org/10.1186/s40200-016-0273-3.

[12] D. Huang, Dietary antioxidants and health promotion, Antioxidants 7 (2018) 9, https://doi.org/10.3390/antiox7010009.

[13] S.K. Bardaweel, M. Gul, M. Alzweiri, A. Ishaqat, H.A. ALSalamat, R. M. Bashatwah, Reactive oxygen species: the dual role in physiological and pathological conditions of the human body, Eurasia J. Med. 50 (2018) 193–201, https://doi.org/10.5152/eurasianjmed.2018.17397.

[14] A. Bhattacharyya, R. Chattopadhyay, S. Mitra, S.E. Crowe, Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases, Physiol. Rev. 94 (2014) 329–354, https://doi.org/10.1152/physrev.00040.2012.

[15] V. Lobo, A. Patil, A. Phatak, N. Chandra, Free radicals, antioxidants and functional foods: Impact on human health, Pharmacogn. Rev. 4 (2010) 118–126, https://doi.org/10.4103/0973-7847.70902.

[16] D.I. Brown, K.K. Griendling, Nox proteins in signal transduction, Free Radic. Biol. Med. 47 (2009) 1239–1253, https://doi.org/10.1016/j.freeradbiomed.2009.07.023.

[17] R. Blomhoff, Dietary antioxidants and cardiovascular disease, Curr. Opin. Lipidol. 16 (2005) 47–54, https://doi.org/10.1097/00041433-200502000-00009.

[18] I. Paur, M.H. Carlsen, B.L. Halvorsen, R. Blomhoff, Antioxidants in herbs and spices, in: I.F.F. Benzie, S. Wachtel-Galor (Eds.), Herbal Medicine: Biomolecular and Clinical Aspects, CRC Press, 2011.

[19] K. Chen, S.E. Craige, J.F. Keaney Jr., Downstream targets and intracellular compartmentalization in Nox signaling, Antioxid. Redox Signal 11 (2009) 2467–2480, https://doi.org/10.1089/ars.2009.2594.

[20] P.S. Brookes, A.L. Levonen, S. Shiva, P. Sarti, V.M. Darley-Usmar, Mitochondria: regulators of signal transduction by reactive oxygen and nitrogen species, Free Radic. Biol. Med. 33 (2002) 755–764, https://doi.org/10.1016/s0891-5849(02)00901-2.

[21] M. Carocho, I.C. Ferreira, A review on antioxidants, prooxidants and related controversy: natural and synthetic compounds, screening and analysis methodologies and future perspectives, Food Chem. Toxicol. 51 (2013) 15–25, https://doi.org/10.1016/j.fct.2012.09.021.

[22] H. Kamata, S.I. Honda, S. Maeda, L. Chang, H. Hirata, M. Karin, Reactive oxygen species promote TNFα-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases, Cell 120 (2005) 649–661, https://doi.org/10.1016/j.cell.2004.12.041.

[23] P.J. Kiley, G. Storz, Exploiting thiol modifications, PLoS Biol. 2 (2004), e400, https://doi.org/10.1371/journal.pbio.0020400.

[24] D. Trachootham, W. Lu, M.A. Ogasawara, N.R.D. Valle, P. Huang, Redox regulation of cell survival, Antioxid. Redox Signal 10 (2008) 1343–1374, https://doi.org/10.1089/ars.2007.1957.

[25] B.L. Tan, M.E. Norhaizan, W.P.P. Liew, H. Sulaiman Rahman, Antioxidant and oxidative stress: a mutual interplay in age-related diseases, Front. Pharmacol. 9 (2018) 1162, https://doi.org/10.3389/fphar.2018.01162.

[26] O.M. Ighodaro, O.A. Akinloye, First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): their fundamental role in the entire antioxidant defence grid, Alex. J. Med. 54 (2018) 287–293, https://doi.org/10.1016/j.ajme.2017.09.001.

[27] I.N. Zelko, T.J. Mariani, R.J. Folz, Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression, Free Radic. Biol. Med. 33 (2002) 337–349, https://doi.org/10.1016/s0891-5849(02)00905-x.

[28] F. Johnson, C. Giulivi, Superoxide dismutases and their impact upon human health, Mol. Asp. Med. 26 (2005) 340–352, https://doi.org/10.1016/j.mam.2005.07.006.

[29] J. Wuerges, J.W. Lee, Y.I. Yim, H.S. Yim, S.O. Kang, K.D. Carugo, Crystal structure of nickel-containing superoxide dismutase reveals another type of active site, Proc. Natl. Acad. Sci. USA 101 (2004) 8569–8574, https://doi.org/10.1073/pnas.0308514101.

[30] S. Shigeoka, T. Ishikawa, M. Tamoi, Y. Miyagawa, T. Takeda, Y. Yabuta, K. Yoshimura, Regulation and function of ascorbate peroxidase isoenzymes, J. Exp. Bot. 53 (372) (2002) 1305–1319, https://doi.org/10.1093/jexbot/53.372.1305.

[31] X. Cao, S.V. Antonyuk, S.V. Seetharaman, L.J. Whitson, A.B. Taylor, S. P. Holloway, R.W. Strange, P.A. Doucette, J.S. Valentine, A. Tiwari, Structures of the G85R variant of SOD1 in familial amyotrophic lateral sclerosis, J. Biol. Chem. 283 (2008) 16169–16177, https://doi.org/10.1074/jbc.M801522200.

[32] P. Chelikani, I. Fita, P.C. Loewen, Diversity of structures and properties among catalases, Cell. Mol. Life Sci. 61 (2004) 192–208, https://doi.org/10.1007/s00018-003-3206-5.

[33] A. Nandi, L.J. Yan, C.K. Jana, N. Das, Role of catalase in oxidative stress-and age-associated degenerative diseases, Oxid. Med. Cell. Longev. 2019 (2019) 1–19, https://doi.org/10.1155/2019/9613090.

[34] H.J. Forman, H. Zhang, A. Rinna, Glutathione: overview of its protective roles, measurement, and biosynthesis, Mol. Asp. Med. 30 (2009) 1–12, https://doi.org/10.1016/j.mam.2008.08.006.

[35] J.D. Hayes, J.U. Flanagan, I.R. Jowsey, Glutathione transferases, Annu. Rev. Pharmacol. Toxicol. 45 (2005) 51–88, https://doi.org/10.1146/annurev.pharmtox.45.120403.095857.

[36] S. Chambial, S. Dwivedi, K.K. Shukla, P.J. John, P. Sharma, Vitamin C in disease prevention and cure: an overview, Indian J. Clin. Biochem. 28 (2013) 314–328, https://doi.org/10.1007/s12291-013-0375-3.

[37] S.J. Padayatty, A. Katz, Y. Wang, P. Eck, O. Kwon, J.H. Lee, S. Chen, C. Corpe, A. Dutta, S.K. Dutta, Vitamin C as an antioxidant: evaluation of its role in disease prevention, J. Am. Coll. Nutr. 22 (2003) 18–35, https://doi.org/10.1080/07315724.2003.10719272.

[38] V.I. Lushchak, Glutathione homeostasis and functions: Potential targets for medical interventions, J. Amino Acids 2012 (2012) 1–26, https://doi.org/10.1155/2012/736837.

[39] G. Noctor, G. Queval, A. Mhamdi, S. Chaouch, C.H. Foyer, Glutathione, Arab. Book 9 (2011) 1–32, https://doi.org/10.1199/table0142.

[40] E. Nassar, C. Mulligan, L. Taylor, C. Kerksick, M. Galbreath, M. Greenwood, R. Kreider, D.S. Willoughby, Effects of a single dose of N-Acetyl-5-methoxytryptamine (Melatonin) and resistance exercise on the growth hormone/IGF-1 axis in young males and females, J. Int. Soc. Sports Nutr. 4 (2007) 1–13, https://doi.org/10.1186/1550-2783-4-14.

[41] K. Back, D.X. Tan, R.J. Reiter, Melatonin biosynthesis in plants: multiple pathways catalyze tryptophan to melatonin in the cytoplasm or chloroplasts, J. Pineal Res. 61 (2016) 426–437, https://doi.org/10.1111/jpi.12364.

[42] J. Vázquez, B. González, V. Sempere, A. Mas, M.J. Torija, G. Beltran, Melatonin reduces oxidative stress damage induced by hydrogen peroxide in Saccharomyces

cerevisiae, Front. Microbiol. 8 (2017) 1066, https://doi.org/10.3389/fmicb.2017.01066.
[43] M.L. Colombo, An update on vitamin E, tocopherol and tocotrienol-perspectives, Molecules 15 (2010) 2103–2113, https://doi.org/10.3390/molecules15042103.
[44] E. Reboul, Vitamin E bioavailability: mechanisms of intestinal absorption in the spotlight, Antioxidants 6 (2017) 95, https://doi.org/10.3390/antiox6040095.
[45] M.G. Traber, J. Atkinson, Vitamin E, antioxidant and nothing more, Free Radic. Biol. Med. 4 (2007) 4–15, https://doi.org/10.1016/j.freeradbiomed.2007.03.024.
[46] H. Jaeschke, G.J. Gores, A.I. Cederbaum, J.A. Hinson, D. Pessayre, J.J. Lemasters, Mechanisms of hepatotoxicity, Toxicol. Sci. 65 (2002) 166–176, https://doi.org/10.1093/toxsci/65.2.166.
[47] T. Grune, V. Darley-Usmar, T.Y. Aw, S. Lamas, Launch of redox biology: a new venue for studies in translational, basic and applied research in the fields of antioxidants, cell signaling and redox therapeutics, Redox Biol. 1 (2013) 17–18, https://doi.org/10.1016/j.redox.2013.01.010.
[48] S.S. Ali, N. Kasoju, A. Luthra, A. Singh, H. Sharanabasava, A. Sahu, U. Bora, Indian medicinal herbs as sources of antioxidants, Food Res. Int. 41 (2008) 1–15, https://doi.org/10.1016/j.foodres.2007.10.001.
[49] M.K. Waqas, A. Shah, N. Akhtar, G. Murtaza, Screening of various botanical extracts for antioxidant activity using DPPH free radical method, Afr. J. Tradit. Complement. Altern. Med. 10 (2013) 452–455, https://doi.org/10.4314/ajtcam.v10i6.9.
[50] S.H. Nile, B. Kumar, S.W. Park, In vitro evaluation of selected benzimidazole derivatives as an antioxidant and xanthine oxidase inhibitors, Chem. Biol. Drug Des. 82 (2013) 290–295, https://doi.org/10.1111/cbdd.12141.
[51] A.M. Pisoschi, A. Pop, C. Cimpeanu, G. Predoi, Antioxidant capacity determination in plants and plant-derived products: a review, Oxid. Med. Cell. Longev. 2016 (2016) 1–36, https://doi.org/10.1155/2016/9130976.
[52] S.B. Iloki-Assanga, L.M. Lewis-Luján, C.L. Lara-Espinoza, A.A. Gil-Salido, D. Fernandez-Angulo, J.L. Rubio-Pino, D.D. Haines, Solvent effects on phytochemical constituent profiles and antioxidant activities, using four different extraction formulations for analysis of Bucida buceras L. and Phoradendron californicum, BMC Res. Notes 8 (2015) 1–14, https://doi.org/10.1186/s13104-015-1388-1.
[53] D.P. Xu, Y. Li, X. Meng, T. Zhou, Y. Zhou, J. Zheng, J.J. Zhang, H.B. Li, Natural antioxidants in foods and medicinal plants: extraction, assessment and resources, Int. J. Mol. Sci. 18 (2017) 96, https://doi.org/10.3390/ijms18010096.
[54] S.H. Nile, S.W. Park, HPTLC analysis, antioxidant, anti-inflammatory and antiproliferative activities of Arisaema tortuosum tuber extract, Pharm. Biol. 52 (2014) 221–227, https://doi.org/10.3109/13880209.2013.831110.
[55] S.H. Nile, S.W. Park, Chromatographic analysis, antioxidant, anti-inflammatory, and xanthine oxidase inhibitory activities of ginger extracts and its reference compounds, Ind. Crop. Prod. 70 (2015) 238–244, https://doi.org/10.1016/j.indcrop.2015.03.033.
[56] F. Alhakmani, S. Kumar, S.A. Khan, Estimation of total phenolic content, in–vitro antioxidant and anti–inflammatory activity of flowers of Moringa oleifera, Asian Pac. J. Trop. Biomed. 3 (2013) 623–627, https://doi.org/10.1016/S2221-1691(13)60126-4.
[57] B. Sagnia, D. Fedeli, R. Casetti, C. Montesano, G. Falcioni, V. Colizzi, Antioxidant and anti-inflammatory activities of extracts from Cassia alata, Eleusine indica, Eremomastax speciosa, Carica papaya and Polyscias fulva medicinal plants collected in Cameroon, PLoS One 9 (2014), e103999, https://doi.org/10.1371/journal.pone.0103999.
[58] S.H. Nile, Y.S. Keum, A.S. Nile, S.S. Jalde, R.V. Patel, Antioxidant, anti-inflammatory, and enzyme inhibitory activity of natural plant flavonoids and their synthesized derivatives, J. Biochem. Mol. Toxicol. 32 (2018), e22002, https://doi.org/10.1002/jbt.22002.
[59] N. Alam, K.N. Yoon, K.R. Lee, H.Y. Kim, P.G. Shin, J.C. Cheong, Y.B. Yoo, M. J. Shim, M.W. Lee, T.S. Lee, Assessment of antioxidant and phenolic compound concentrations as well as xanthine oxidase and tyrosinase inhibitory properties of different extracts of Pleurotus citrinopileatus fruiting bodies, Mycobiology 39 (2011) 12–19, https://doi.org/10.4489/MYCO.2011.39.1.012.
[60] S. Mahernia, K. Bagherzadeh, F. Mojab, M. Amanlou, Urease inhibitory activities of some commonly consumed herbal medicines, Iran. J. Pharm. Res. 14 (2015) 943–947.
[61] S.H. Nile, A.S. Nile, Y.S. Keum, K. Sharma, Utilization of quercetin and quercetin glycosides from onion (Allium cepa L.) solid waste as an antioxidant, urease and xanthine oxidase inhibitors, Food Chem. 235 (2017) 119–126, https://doi.org/10.1016/j.foodchem.2017.05.043.
[62] K. Thenmozhi, N. Anusuya, M. Ajmal Ali, S. Jamuna, K. Karthika, A. Venkatachalapathi, F.M. Al-Hemaid, M.A. Farah, S. Paulsamy, Pharmacological credence of the folklore use of Bauhinia malabarica in the management of jaundice, Saudi J. Biol. Sci. 25 (2018) 22–26, https://doi.org/10.1016/j.sjbs.2017.08.001.
[63] R. Javaid, M. Aslam, Q. Nizami, R. Javaid, Role of antioxidant herbal drugs in renal disorders: an overview, Free Radic. Antioxid. 2 (2012) 2–5, https://doi.org/10.5530/ax.2012.2.2.
[64] H. Ghaffari, M. Venkataramana, S.C. Nayaka, B.J. Ghassam, N. Angaswamy, S. Shekar, K.K. Sampath Kumara, H.S. Prakash, Hepatoprotective action of Orthosiphon diffusus (Benth.) methanol active fraction through antioxidant mechanisms: an in vivo and in vitro evaluation, J. Ethnopharmacol. 149 (2013) 737–744, https://doi.org/10.1016/j.jep.2013.07.034.
[65] R. Hamidpour, S. Hamidpour, M. Hamidpour, M. Shahlari, M. Sohraby, N. Shahlari, R. Hamidpour, Russian olive (Elaeagnus angustifolia L.): from a variety of traditional medicinal applications to its novel roles as active antioxidant, anti-inflammatory, anti-mutagenic and analgesic agent, J. Tradit. Complement. Med. 7 (2017) 24–29, https://doi.org/10.1016/j.jtcme.2015.09.004.
[66] Q. Li, Y. Tu, C. Zhu, W. Luo, W. Huang, W. Liu, Y. Li, Cholinesterase, β-amyloid aggregation inhibitory and antioxidant capacities of Chinese medicinal plants, Ind. Crop. Prod. 108 (2017) 512–519, https://doi.org/10.1016/j.indcrop.2017.07.001.
[67] S.K. Ali, A.R. Hamed, M.M. Soltan, U.M. Hegazy, E.E. Elgorashi, I.A. El-Garf, A. A. Hussein, In-vitro evaluation of selected Egyptian traditional herbal medicines for treatment of Alzheimer disease, 121-121, BMC Complement. Altern. Med. 13 (2013), https://doi.org/10.1186/1472-6882-13-121.
[68] E.J. Park, C.H. Jeon, G. Ko, J. Kim, D.H. Sohn, Protective effect of curcumin in rat liver injury induced by carbon tetrachloride, J. Pharm. Pharmacol. 52 (2000) 437–440, https://doi.org/10.1211/0022357001774048.
[69] Y.Z. Gong, F. Xu, Q. Kang, Hepatoprotective effect of Mitragynarotundifolia Kuntze on CCl4-induced acute liver injury in mice, Afr. J. Pharm. Pharmacol. 6 (2012) 330–335, https://doi.org/10.5897/AJPP11.766.
[70] X. Cui, X. Gu, W. Kang, Antioxidant activity in vitro and hepatoprotective effects in vivo of compound lobelia, Afr. J. Tradit. Complement. Altern. Med. 13 (2016) 114–122, https://doi.org/10.21010/ajtcam.v13i5.15.
[71] I.O. Ishola, A.A. Akinyede, A.K. Robert, S.A. Omilabu, Hepatoprotective and antioxidant activities of Hepacare, a herbal formulation against carbon tetrachloride-induced liver injury, Drug Res. 65 (2015) 30–39, https://doi.org/10.1055/s-0034-1371829.
[72] S. Gianfaldoni, G. Tchernev, J. Lotti, U. Wollina, F. Satolli, M. Rovesti, K. França, T. Lotti, Unconventional treatments for vitiligo: are they (un) satisfactory? Open Access Maced. J. Med. Sci. 6 (2018) 170–175, https://doi.org/10.3889/oamjms.2018.038.
[73] O. Neamsuvan, P. Bunmee, A survey of herbal weeds for treating skin disorders from Southern Thailand: Songkhla and Krabi Province, J. Ethnopharmacol. 193 (2016) 574–585, https://doi.org/10.1016/j.jep.2016.09.048.
[74] H. Uchi, M. Yasumatsu, S. Morino-Koga, C. Mitoma, M. Furue, Inhibition of aryl hydrocarbon receptor signaling and induction of NRF2-mediated antioxidant activity by cinnamaldehyde in human keratinocytes, J. Dermatol. Sci. 85 (2017) 36–43, https://doi.org/10.1016/j.jdermsci.2016.10.003.
[75] K. Kant, U.R. Lal, M. Ghosh, In silico prediction and wet lab validation of Arisaema tortuosum (Wall.) Schott extracts as antioxidant and anti-breast cancer source: a comparative study, S786-s790, Pharmacogn. Mag. 13 (2018), https://doi.org/10.4103/pm.pm_69_17.
[76] N.K. Yadav, K.S. Saini, Z. Hossain, A. Omer, C. Sharma, J.R. Gayen, P. Singh, K. R. Arya, R.K. Singh, Saraca indica bark extract shows in vitro antioxidant, antibreast cancer activity and does not exhibit toxicological effects, Oxid. Med. Cell Longev. 2015 (2015), 205360, https://doi.org/10.1155/2015/205360.
[77] S.E. Park, W.T. Shin, C. Park, S.H. Hong, G.Y. Kim, S.O. Kim, C.H. Ryu, S.H. Hong, Y.H. Choi, Induction of apoptosis in MDA-MB-231 human breast carcinoma cells with an ethanol extract of Cyperus rotundus L. by activating caspases, Oncol. Rep. 32 (2014) 2461–2470, https://doi.org/10.3892/or.2014.3507.
[78] P. Governa, G. Baini, V. Borgonetti, G. Cettolin, D. Giachetti, A.R. Magnano, E. Miraldi, M. Biagi, Phytotherapy in the management of diabetes: a review, Molecules 23 (2018) 105, https://doi.org/10.3390/molecules23010105.
[79] R. Latha, P. Shanthi, P. Sachdanandam, Protective role of Kalpaamruthaa in type II diabetes mellitus-induced cardiovascular disease through the modulation of protease-activated receptor-1, Pharmacogn. Mag. 11 (2015) S209–S216, https://doi.org/10.4103/0973-1296.157739.
[80] J.A. Junejo, M. Rudrapal, L.M. Nainwal, K. Zaman, Antidiabetic activity of hydro-alcoholic stem bark extract of Callicarpa arborea Roxb. with antioxidant potential in diabetic rats, Biomed. Pharmacother. 95 (2017) 84–94, https://doi.org/10.1016/j.biopha.2017.08.032.
[81] S. Tiong, C. Looi, H. Hazni, A. Arya, M. Paydar, W. Wong, S.C. Cheah, M. Mustafa, K. Awang, Antidiabetic and antioxidant properties of alkaloids from Catharanthus roseus (L.) G. Don, Molecules 18 (2013) 9770–9784, https://doi.org/10.3390/molecules18089770.
[82] D.C. D'Souza, R. Radhakrishnan, E. Perry, S. Bhakta, N.M. Singh, R. Yadav, D. Abi-Saab, B. Pittman, S.K. Chaturvedi, M.P. Sharma, M. Bell, C. Andrade, Feasibility, safety, and efficacy of the combination of D-serine and computerized cognitive retraining in schizophrenia: an international collaborative pilot study, Neuropsychopharmacology 38 (2013) 492–503, https://doi.org/10.1038/npp.2012.208.
[83] M. Ermilov, E. Gelfin, R. Levin, P. Lichtenberg, K. Hashimoto, D.C. Javitt, U. Heresco-Levy, A pilot double-blind comparison of d-serine and high-dose olanzapine in treatment-resistant patients with schizophrenia, Schizophr. Res. 150 (2013) 604–605, https://doi.org/10.1016/j.schres.2013.09.018.
[84] E. Ernst, Serious psychiatric and neurological adverse effects of herbal medicines – a systematic review, Acta Psychiatr. Scand. 108 (2003) 83–91, https://doi.org/10.1034/j.1600-0447.2003.00158.x.
[85] P. Singh, D. Singh, R.K. Goel, Ficus religiosa L. figs: a potential herbal adjuvant to phenytoin for improved management of epilepsy and associated behavioral comorbidities, Epilepsy Behav. 41 (2014) 171–178, https://doi.org/10.1016/j.yebeh.2014.10.002.
[86] J.R. Liu, G.F. Chen, H.N. Shih, P.C. Kuo, Enhanced antioxidant bioactivity of Salvia miltiorrhiza (Danshen) products prepared using nanotechnology, Phytomedicine 15 (2008) 23–30, https://doi.org/10.1016/j.phymed.2007.11.012.
[87] I. Ocsoy, D. Tasdemir, S. Mazicioglu, W. Tan, Nanotechnology in plants. Advances in Biochemical Engineering/Biotechnology, Springer Verlag, 2018.

[88] M. Shakeel, F. Jabeen, R. Iqbal, A.S. Chaudhry, S. Zafar, M. Ali, M.S. Khan, A. Khalid, S. Shabbir, M.S. Asghar, Assessment of titanium dioxide nanoparticles (TiO2-NPs) induced hepatotoxicity and ameliorative effects of Cinnamomum cassia in Sprague-Dawley rats, Biol. Trace Elem. Res. 182 (2018) 57–69, https://doi.org/10.1007/s12011-017-1074-3.
[89] U. Nagaich, S. Chauhan, N. Gulati, Antioxidant and antibacterial potential of silver nanoparticles: biogenic synthesis utilizing apple extract, J. Pharm. Pharmacol. 2016 (2016) 1–8, https://doi.org/10.1155/2016/7141523.
[90] M.E. Barbinta-Patrascu, I.R. Bunghez, S.M. Iordache, N. Badea, R.C. Fierascu, R. M. Ion, Antioxidant properties of biohybrids based on liposomes and sage silver nanoparticles, J. Nanosci. Nanotechnol. 13 (2013) 2051–2060, https://doi.org/10.1166/jnn.2013.6857.
[91] H. Park, S. Kim, S. Kim, Y. Song, K. Seung, D. Hong, G. Khang, D. Lee, Antioxidant and anti-Inflammatory activities of hydroxybenzyl alcohol releasing biodegradable polyoxalate nanoparticles, Biomacromolecules 11 (2010) 2103–2108, https://doi.org/10.1021/bm100474w.
[92] C. Chang, T. Wang, Q. Hu, M. Zhou, J. Xue, Y. Luo, Pectin coating improves physicochemical properties of caseinate/zein nanoparticles as oral delivery vehicles for curcumin, Food Hydrocoll. 70 (2017) 143–151, https://doi.org/10.1016/j.foodhyd.2017.03.033.
[93] S. Zhang, Y. Han, Preparation, characterisation and antioxidant activities of rutin-loaded zein-sodium caseinate nanoparticles, PLoS One 13 (2018), e0194951, https://doi.org/10.1371/journal.pone.0194951.
[94] P. Ganesan, P. Ramalingam, G. Karthivashan, Y.T. Ko, D.K. Choi, Recent developments in solid lipid nanoparticle and surface-modified solid lipid nanoparticle delivery systems for oral delivery of phyto-bioactive compounds in various chronic diseases, Int. J. Nanomed. 13 (2018) 1569–1583, https://doi.org/10.2147/IJN.S155593.
[95] H. Zhang, X. Zou, Q. Huang, X. Zhong, Z. Huang, Effects of Kudingcha nanoparticles in hyperlipidaemic rats induced by a high fat diet, Cell. Physiol. Biochem. 45 (2018) 2257–2267, https://doi.org/10.1159/000488171.
[96] T. Pal, S. Mohiyuddin, G. Packirisamy, Facile and green synthesis of multicolor fluorescence carbon dots from Curcumin: in vitro and in vivo bioimaging and other applications, ACS Omega 3 (2018) 831–843, https://doi.org/10.1021/acsomega.7b01323.
[97] A. Sachdev, P. Gopinath, Green synthesis of multifunctional carbon dots from coriander leaves and their potential application as antioxidants, sensors and bioimaging agents, Analyst 140 (2015) 4260–4269, https://doi.org/10.1039/C5AN00454C.
[98] S. Mignani, J. Rodrigues, H. Tomas, M. Zablocka, X. Shi, A.M. Caminade, J. P. Majoral, Dendrimers in combination with natural products and analogues as anti-cancer agents, Chem. Soc. Rev. 47 (2018) 514–532, https://doi.org/10.1039/C7CS00550D.
[99] K.N. Kontogiannopoulos, A.N. Assimopoulou, S. Hatziantoniou, K. Karatasos, C. Demetzos, V.P. Papageorgiou, Chimeric advanced drug delivery nano systems (chi-aDDnSs) for shikonin combining dendritic and liposomal technology, Int. J. Pharm. 422 (2012) 381–389, https://doi.org/10.1016/j.ijpharm.2011.09.031.
[100] M.H. Farzaei, R. Bahramsoltani, Z. Abbasabadi, R. Rahimi, A comprehensive review on phytochemical and pharmacological aspects of Elaeagnus angustifolia L, J. Pharm. Pharmacol. 67 (2015) 1467–1480, https://doi.org/10.1111/jphp.12442.
[101] Y. Cui, P. Liu, R. Chen, Studies on the chemical constituents of Spatholobus suberectus Dunn, Acta Pharm. Sin. 37 (2002) 784–787.
[102] M. Xu, L. Zhang, P. Li, C. Wang, Y. Shi, Network pharmacology used to decode potential active ingredients in Ferula assafoetida and mechanisms for the application to Alzheimer's disease, J. Tradit. Chin. Med. Sci. 7 (2020) 199–209, https://doi.org/10.1016/j.jtcms.2020.04.002.
[103] S. Ali, A. Hamed, M. Soltan, A. El-Halawany, U. Hegazy, A. Hussein, Kinetics and molecular docking of vasicine from Adhatoda vasica: an acetylcholinesterase inhibitor for Alzheimer's disease, South Afr. J. Bot. 104 (2016) 118–124, https://doi.org/10.1016/j.sajb.2015.09.021.
[104] D.A. Ofusori, A.O. Adejuwon, Histopathological studies of acute and chronic effects of Calliandra portoricensis leaf extract on the stomach and pancreas of adult Swiss albino mice, Asian Pac. J. Trop. Biomed. 1 (2011) 182–185, https://doi.org/10.1016/S2221-1691(11)60023-3.
[105] R. Tewari, M. Gupta, F. Ahmad, P.K. Rout, L. Misra, A. Patwardhan, R. Vasudeva, Extraction, quantification and antioxidant activities of flavonoids, polyphenols and pinitol from wild and cultivated Saraca asoca bark using RP-HPLC-PDA-RI method, Ind. Crop. Prod. 103 (2017) 73–80, https://doi.org/10.1016/j.indcrop.2017.03.036.
[106] O.A. Lawal, A.O. Oyedeji, Chemical composition of the essential oils of Cyperus rotundus L. from South Africa, Molecules 14 (2009) 2909–2917, https://doi.org/10.3390/molecules14082909.
[107] M.C. Milanez, G.B.L. de Freitas, R.P. Pereira, J.S. Bonini, Ginkgo biloba L.: phytochemical components and antioxidant activity, Afr. J. Pharm. Pharmacol. 9 (2015) 950–955, https://doi.org/10.5897/AJPP2015.4373.
[108] S. Miraj, K. Rafieian, S. Kiani, Melissa officinalis L: a review study with an antioxidant prospective, J. Evid. Based Complement. Altern. Med. 22 (2017) 385–394, https://doi.org/10.1177/2156587216663433.
[109] S.K. El Euch, D.B. Hassine, S. Cazaux, N. Bouzouita, J. Bouajila, Salvia officinalis essential oil: chemical analysis and evaluation of anti-enzymatic and antioxidant bioactivities, South Afr. J. Bot. 120 (2019) 253–260, https://doi.org/10.1016/j.sajb.2018.07.010.
[110] J. Zhang, S.J. An, J.Q. Fu, P. Liu, T.M. Shao, M. Li, X. Li, Z. Jiao, X.Q. Chai, Mixed aqueous extract of Salvia miltiorrhiza reduces blood pressure through inhibition of vascular remodelling and oxidative stress in spontaneously hypertensive rats, Cell. Physiol. Biochem. 40 (2016) 347–360, https://doi.org/10.1159/000452550.
[111] D. Huang, J.G. Xu, J.X. Liu, H. Zhang, Q. Hu, Chemical constituents, antibacterial activity and mechanism of action of the essential oil from Cinnamomum cassia bark against four food-related bacteria, Microbiology 83 (2014) 357–365, https://doi.org/10.1134/S0026261714040067.
[112] A. Önder, Coriander and its phytoconstituents for the beneficial effects, in: Hany El-Shemy (Ed.), Potential of Essential Oils, Intech Open, 2018, pp. 165–185.
[113] ⟨https://clinicaltrials.gov⟩. (Accessed 12th April 2022).