Review Article
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Phytochemicals as a potential source for anti-microbial, anti-oxidant and wound healing - a review

Abstract

Phytochemicals are known for their therapeutic properties in treating various diseases and disorders. It also holds great promise for discovery and development of new pharmaceuticals in diverse human ailments. A large number of medicinal plants are claimed to possess the anti-biotic, anti-oxidant and wound healing properties in the traditional system. The phytochemical investigations of traditionally used medicinal plants have shown the diversified useful compound classes like alkaloid, phenolic, tannin, terpene, steroid, flavonoid, glycoside, and fatty acid. These phytochemical components play an important role in scavenging free radicals, fighting infection and promoting the faster wound-healing process. Phytochemicals can serve as a cost-effective alternative therapeutic agent for human diseases. This review mainly focuses on phytochemicals and their role as anti-microbial, anti-oxidant and wound healing agent.

Keywords: phytochemicals, wound healing, anti-microbial, anti-oxidant

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Introduction

Higher plants have provided the necessities of life such as food, shelter, and clothing to humanity from the very beginning of human civilization. In addition to that, they have also been the most important source of medicine for the treatment of various ailments since time immemorial. Although there has been considerable development in the areas of synthetic drug chemistry and antibiotics, plants still occupy an important place in the traditional and modern system of medicine. Realizing the toxic effects of the synthetic drugs, the herbal medicine and the foods that derived from plants has become an alternative even in well-developed countries. Traditional medicinal plants with rich medicinal value are utilized as folk remedies and as a pharmaceutical formulation in the modern system of medicine. Some of the main phytochemicals that medicinal plants contain includes polyphenols, alkaloids, flavonoids, steroids, tannins, and terpenoids.[1]

The ancient development of traditional medicinal systems can be traced back to some 60,000 years ago.[2] All well-developed countries have been using herbal drugs[3] and according to the WHO, almost 75% of the world's population has incorporated the use of medicinal products in their life as an alternate of allopathy drugs.[4] It is noted that 35% of all drugs suggested and prescribed today are obtained from medicinal plants.[4,5]

Among the modern drugs in use today, about 40 % are of natural origin.[6] Due to advancement in the newer technologies, the production of plant-derived crude drugs for use as herbal remedies or raw materials in the pharmaceutical industry has increased manifolds. The drugs of natural origin used in modern medicine are pure, chemically well-defined compounds that are either used directly or are modified after suitable chemical or microbiological methods before their use as a drug.

Herbal medicines with rich bioactive phytochemicals could be useful and alternative therapeutic agents for the people who live in places where conventional drugs cannot be supplied to or who cannot afford conventional treatment.[7,8] Still, modern scientific methods must evaluate the therapeutic effects of specific herbal compounds.[9]

Phytochemicals and its classification

Phytochemicals are what natural bioactive compounds that appear to have significant physiological effects in the human body and they cover a wide range of chemical entities such as, flavonoids, polyphenols, saponins, steroids, vitamins, among others. Phytochemicals are classified as primary or secondary constituents, depending on their role in plant metabolism (Figure 1) (Figure 2).

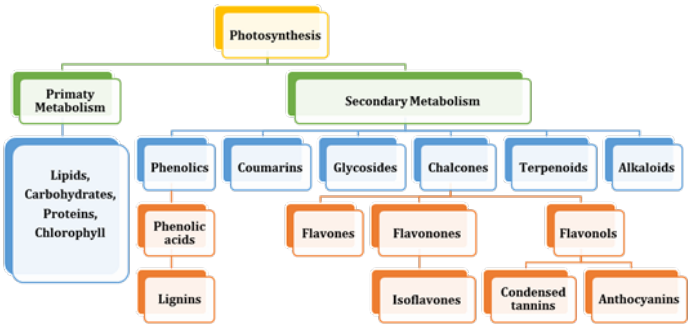

Figure 1 Relationship between primary and secondary metabolism in plants.

Alkaloids

Alkaloids contain heterocyclic nitrogen atoms, are basic in character which formed salts with an acid. Almost all the alkaloids have a bitter taste. Alkaloids are classified depending on the type of heterocyclic ring system present in the molecule (Table 1).

Flavonoids

Flavonoids are polyphenolic compounds that are ubiquitous among vascular plants and occur as aglycones, glucosides, and methylated derivatives. The six-membered ring condensed with the benzene ring is either pyrone (flavones and flavonols) or its dihydro derivative (flavanones and flavan-3-ols). The position of the

benzenoid substituent divides the flavonoids into two classes: flavone and isoflavone. Most flavonoids occur naturally associated with sugar in conjugated form and, within any one class, may be characterized as monoglycosidic, diglycosidic, etc. The glycosidic linkage is normally located at position 3 or 7 and the carbohydrate unit can be L-rhamnose, D-glucose, galactose or arabinose.[10]

Classification of Phytochemicals	Alkaloids
	Anthocyanins
	Coumarins
	Flavonoids
	Fatty acids
	Lactones
	Polypeptides
	Polyphenols
	Tannins
	Terpenoids
	Saponins
	Sterols

Figure 2 Classifications of Phytochemicals.

Table 1 Class of alkaloids

Class	Compounds
Pyrrolidine alkaloids	Hygrine
Pyridine alkaloids	Coniine, Piperine, Isopelletierine
Pyrrolidine-pyridine alkaloids	Myosmine, Nicotine
Pyridine-piperidine alkaloids	Anabasine
Quinoline Alkaloids	Quinine, Primaquinine
Isoquinoline alkaloids	Narcotine, Papaverine, Morphine, Codeine, Heroin

Phenolic acids

Phenolic acids possess one carboxylic acid functional group. Naturally occurring phenolic acids contain two distinctive carbon frameworks: the hydroxycinnamic and hydroxybenzoic structures. Hydroxycinnamic acid compounds are produced as simple esters with glucose/hydroxycarboxylic acids. Biogenetically, phenolic compounds proceed of two metabolic pathways: the shikimic acid pathway where, mainly, phenylpropanoids are formed and the acetic acid pathway, in which the main products are the simple phenol[11] Most plants phenolic compounds are synthesized through the phenylpropanoid pathway.[12] The combination of both pathways leads to the formation of flavonoids, the most plentiful group of phenolic compounds in nature (Table 2).[11]

Saponins

Saponins are a group of plant secondary metabolites found to form stable foam in aqueous solutions such as soap. Saponins include compounds that are glycosylated steroids, triterpenoids, and steroid alkaloids. Two main types of steroid aglycones are known, spirostan and furostan derivatives. The carbohydrate part consists of one or more sugar moieties containing glucose, galactose, xylose, arabinose, rhamnose, or glucuronic acid glycosidically linked to a sapogenin (aglycone). Saponins that have one sugar molecule attached at the C-3 position are called monodesmoside saponins, and those that have a minimum of two sugars, one attached to the C-3 and one at C-22, are called bidesmoside saponins.[13]

Table 2 Classes of phenolic acids

Class	Compounds
Hydroxy cinnamic acids	p-coumaric acid, Ferulic acid, Caffeic acid, Sinapic acid
Hydroxy benzoic acid	Gallic acid, Protocatechuic acid, Vanillic acid

Tannins

Tannins are a heterogeneous group of high molecular weight polyphenolic compounds with the capacity to form reversible and irreversible complexes with proteins, polysaccharides, alkaloids, nucleic acids, and minerals, etc (Figure 3).

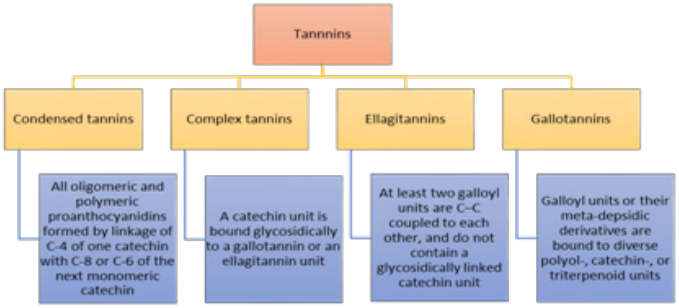

Figure 3 Classification of tannins.

Terpenoids

The terpenoids derived from five-carbon isoprene units. Most of the terpenoids have multicyclic structures that differ from one another by their functional groups and basic carbon skeletons[14] Terpenes are widespread in nature, mainly in plants as constituents of essential oils. Their building block is the hydrocarbon isoprene, CH_2=C(CH_3)-CH=CH_2. Terpene hydrocarbons, therefore, have molecular formula (C_5H_8) n and they are classified according to the number of isoprene units (Table 3) (Table 4).[15]

Table 3 Class of terpenes

Class	Compounds
Monoterpenoids	Eucalyptol, Citral, Camphor, Pinene, Limonene, Geranyl pyrophosphate,
Diterpenes	Cembrene, Kahweol, Taxadiene, Cafestol. Retinol, Retinal, Phytol
Triterpenes	Lanosterol, Squalene
Tetraterpenoids	alpha, beta and gamma carotenes
Sesquiterpenes	Artemisinin, Bisabolol, Fernesol, Eudesmol,
Hemiterpenoids	Isoprene, Isovaleric acid, Prenol

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Table 4 Solvents used to extract major phytochemicals

Acetone	Chloroform	Dichloro-Methanol	Ethanol	Ether	Methanol	Water
Flavonols	Flavonoids	Terpenoids	Alkaloids	Alkaloids	Anthocyanins	Anthocyanins
	Terpenoids		Flavonol	Coumarins	Flavones	Lectins
			Polyacetylene	Fatty acids	Lactones	Polypeptides
			Polyphenols	Terpenoids	Polyphenols	Saponins
			Sterols		Phenones	Starches
			Tannins		Quassinoids	Tannins
			Terpenoids		Saponins	Terpenoids
					Tannins	
					Terpenoids	
					Totarol	
					Xanthoxyllines	

Phytochemical as biomedicine

A natural product can be an entire organism such as a plant or an animal or a microorganism or it can also be a part of it such as a leaf or a flower of a plant or an isolated gland or an organ of an animal.[6] The healing or poisonous properties of plants have been explored since long by humanity. The knowledge of these plants has been passed from one generation to another. Herbal medicines and their preparations have been commonly used for more than 1000 years in countries like India, Japan, China, Korea, etc.,[16] The wound healing properties of the various phytochemicals are due to their inhibition of platelet aggregation, anti-inflammatory, anti-microbial, anti-oxidative activities and that reduce the risk of wound disorders. Numerous studies have been investigated the anti-microbial, anti-oxidant and wound healing agents in an effort to facilitate their use as phytomedicines in the pharmaceutical industry (Figure 4).[17–31]

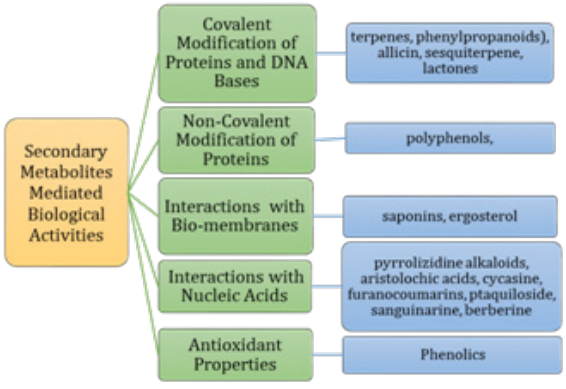


Figure 4 Secondary Metabolites mediated biological activities.

Anti-microbial phytochemicals

Some phytochemicals are well known for their anti-microbial properties which are of major significance to a therapeutic level of treatments.[32] Medicinal plant and their extracts were widely used for the treatment of all the infectious diseases and it forms the basis for all Indian systems of medicine. The effect of medicinal plant and their extracts on microbial pathogens has been studied worldwide.[33,34] The screening of natural products and extracts for anti-microbial activity has clearly shown that medicinal plants represent a potential source of newly invented antibiotics.[35] The genetic ability of microbial pathogens becoming resistant to widely used antibiotics became a major threat to humans worldwide.[36] The use of medicinal plants and the phytochemical components contained in their extract can be a significant alternate in therapeutics and also be helpful in dealing with the threats of multi-drug resistant microbial pathogens.[37] Crude extracts of some traditionally known herbal drugs are used to control microbial pathogens.[38] Anti-microbial components are used in the microbial infection management which may occur in acute and chronic wounds (Figure 5) (Figure 6).[39]

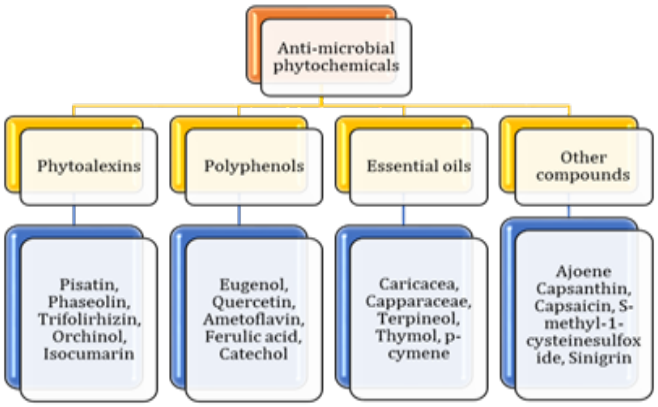
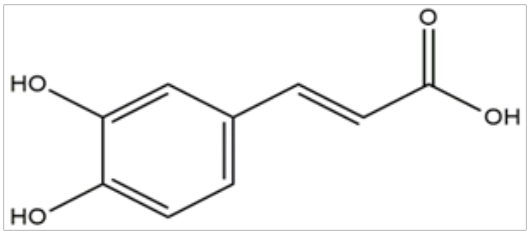


Figure 5 Anti-microbial phytochemicals.



Caffeic acid

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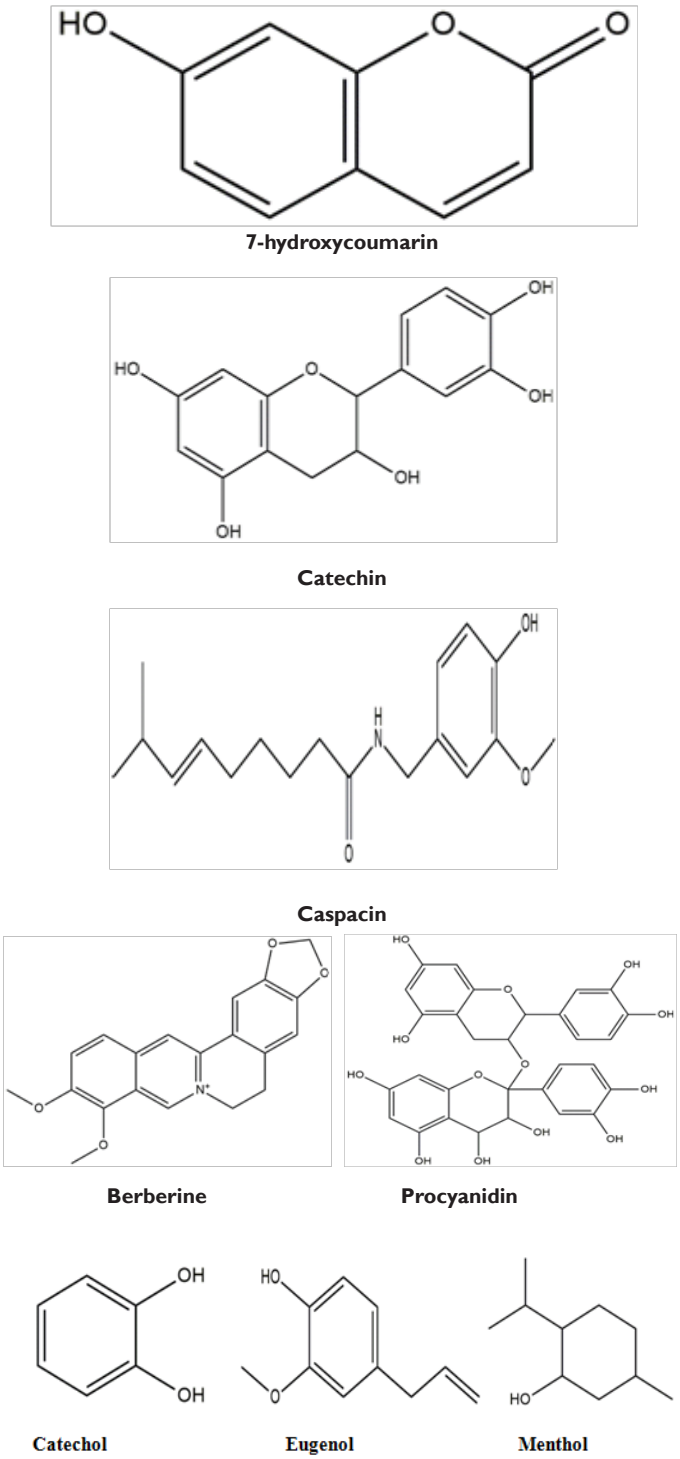

Figure 6 Phytochemical compounds as antimicrobial agents.

Anti-oxidant phytochemicals

Anti-oxidant is a defence system through which a human body is getting protected from oxidative damage of free radicals.[40] Excess in the generation of free radicals leads to cellular stress that can damage the DNA, proteins, and other cellular structure and function.[41]

Reactive Oxygen Species (ROS) are a group of free radicals, reactive molecules, and ions that are derived from O_2. ROS include free radicals such as superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), as well as non-radical molecules like hydrogen peroxide (H_2O_2) and so forth. Medicinal plants have become the potential sources of natural anti-oxidants and produce a number of anti-oxidative compounds that have medicinal and therapeutic properties. Drug formulations that contain anti-oxidant components are widely used for the treatment and prevention of many infectious and complex diseases. It is reported that antioxidants prevent oxidative stress caused by ROS and free radicals.[42] In nature, there is a wide variety of naturally occurring anti-oxidants which are different in their composition, physical and chemical properties, mechanisms and site of action. Medicinal plants rich in flavonoids, vitamins, polyphenols, and anthocyanins are reported to possess remarkable anti-oxidant activity. Anti-oxidant activity is neither restricted to a particular part of the plant nor the specific families (Figures 6–9).

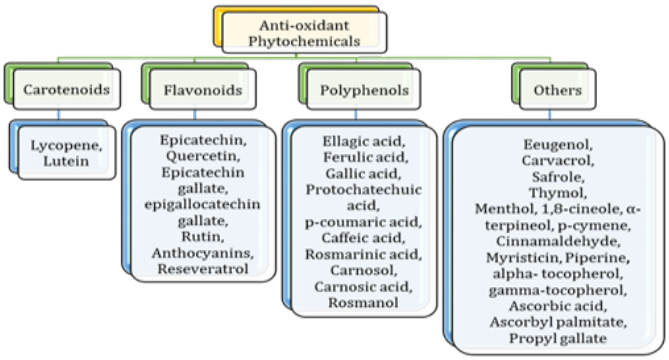

Figure 7 Anti-oxidant phytochemicals.

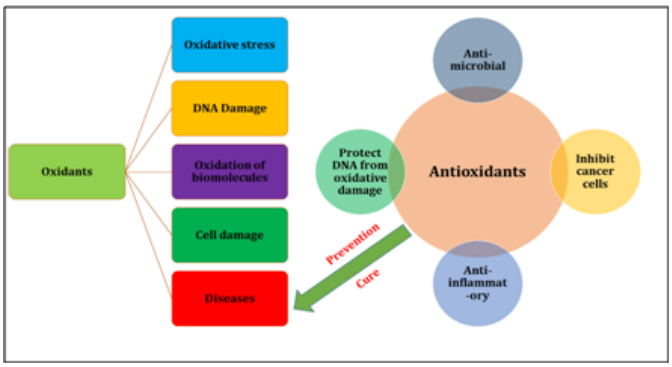

Figure 8 Role of anti-oxidants in preventing diseases.

Wound healing phytochemicals

Wound healing is a complex but a natural process characterized by inflammatory phase, proliferative phase and maturation phase.[43] More than a million people suffer from burn injuries annually[7,44] Wound healing is commonly discussed in the science and medical literature and always there is a need for effective healing medication. In wound injuries, allergic reactions and skin irritations are the most important adverse effects of topical antiseptic agents and disinfectants, which reduce the rate of skin repair and increase the rehabilitation period.[7] The traditional formulation of wound medicine, especially the herbal and other medicinal products deployed worldwide, are still under scientific evaluation for their properties in the treatment of wounds.

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Various herbal drugs and herbal formulations have been widely used in the treatment of wounds for years. Over the past 35 years, the knowledge regarding wound healing process has increased drastically. The development of novel and exciting technologies that accelerate normal wound healing process has come. Several natural products such as alkaloids, tannins, flavonoids, terpenes, promote the healing process.[45] Herbal medicines encourage fighting against infection and accelerating the healing of wounds. The future of science and technology in wound care holds a great promise. Studies on traditional and medicinal plants confirmed that herbal formulations and the drugs derived from medicinal plants exhibit very fewer side effects than synthetic drugs.[39,46] The herbal drugs and herbal formulations for wound healing are affordable and cheap (Table 5).

Table 5 Wound healing phytochemical compounds

S.No	Source	Chemical compounds
1	Acalypha indica	Acalyphin, acalyphamide, acalyphal acetate, aurantiamide, succinimide and flindersin
2	Anacardium occidentale	Cardol, anacardic acid, anacardein, occidentoside, campesterol, ß-sitosterol and Stigmasterol
3	Areca catechu	Arecoline, choline, arecaine, guvacin, aricaidinecatechu and α-catechin
4	Arnebia densiflora	Shikonin, Berberine
5	Berberis lyceum	Berberine
6	Calotropis gigantean	Calotropin, akundarin, uscharin, calotoxin, calactin, α, ß calotropeol, ß-amyrin, giganteol and isogiganteol
7	Centaurea ainetensis	Salograviolide
8	Centella asiatica	Asiaticoside, asiatic acid, and madecassic acid
9	Cleome viscosa	Viscosic acid, viscosin, cleomiscosin A, B, C & D, cleosandrin, cleomeolide
10	Curcuma longa	Curcumin
11	Elephantopus scaber	Sesquiterpene lactones deoxyelephantopin, isodeoxyelephantopin, scabertopin, epifriedelinol, lupeol, stigmasterol
12	Euphorbia hirta	Euphorbia A & B, rutin, gallic acid, quercitrin, l-inositol, kaempferol, xanthorhamin
13	Ficus bengalensis	Bengalenoside, leucocyandin, perlargonidin, leucopelargonin, leucodelphinidin derivatives, caoutchouc, tannins
14	Ficus racemose	Racemosic acid, gluanol acetate, caoutchouc, tannins, ß-sitosterol, stigmasterol, friedelin, hentriacontane
15	Ixora coccinea	Lupeol, fatty ester, ursolic, oleanolic, stearic, oleic, linoleic acids, sitosterol
16	Jasminum auriculatum	Lupeol, jasminol
17	Lawsonia inermis	Lawsochylin A, lawsonaphthoate A, luteolin, apigenin, cytochalasin B, coumaric acid, 2-methoxy-3-methyl-1,4-naphthoquinone, apiin, lawsone, apigenin, luteolin, cosmosiin
18	Morinda pubescens	Morindin, morindone, rubiadin, anthraquinones
19	Pinus densiflora	Pinosylvin
20	Pistacia terebinthus	Masticadienonic acid, masticadienolic acid, morolic acid
21	Punica granatum	granatin B, punicalagin, punicalin, strictinin A
22	Rosa indica	Indomethacin
23	Terminalia bellirica	Gallo-tannic acids, termilignan, thannilignan
24	Others	Borneol, Thymol, Genipin, a-Terpineol, Aucubin

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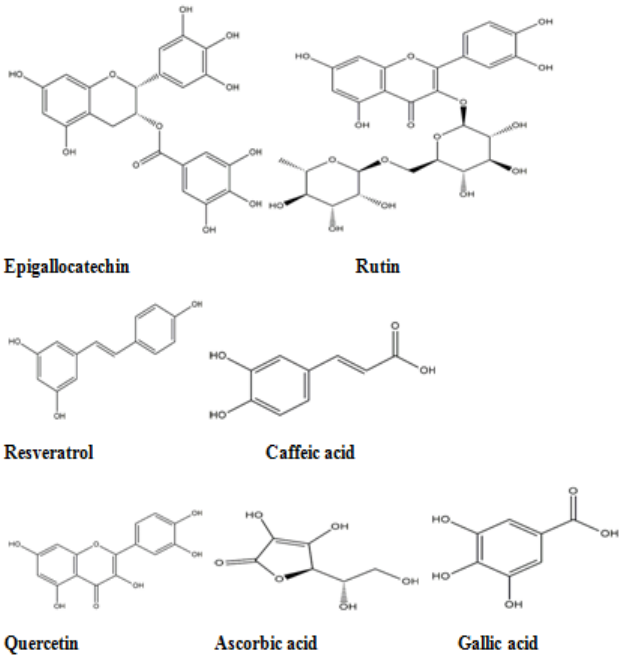

Figure 9 Phytochemical compounds as antioxidant agents.

In silico approach of phytochemicals- a design of better drugs

In silico approaches are useful at the initial stage of drug discovery process. The application of QSAR is extended to molecular design, prediction of different biological activities, lead compound optimization and virtual screening, classification, diagnosis and elucidation of mechanisms of drug action, toxicity prediction of environmental toxicants and prediction of drug-induced toxicity.[47] Phytochemistry approaches are being applied to create screening libraries that closely resemble drug-like compounds. *In silico* techniques such as QSAR (quantitative structure-activity relationships), pharmacophore and virtual screening play a major role in accelerating steps for the better drug design.[48] QSAR models have been built for a wide variety of anti-microbial, anti-oxidant and wound healing phenolic compounds and flavonoids (such as coumarins, lignans, stilbenes, curcuminoids, and tannins) derived from traditional medicinal plants.[49] It is important to stress that natural products differ from synthetic active molecules (e.g., number of aromatic rings, size, flexibility), that are mainly found in biological databases, such as PubChem[50] and CHEMBL.[51] Furthermore, it is a must to evaluate their datasets for compatibility (Table 6) (Table 7).[52,53]

Table 6 Phytochemical compounds- structure, mechanism and therapeutic uses

Class	Compounds	Mechanism, biological and therapeutic uses
Phenolic acids	p-Coumaric acid	• Anti-Infective agent • Anti-oxidant • Contraceptive agent • Free Radical Scavengers, • Protect Pancreatic Islets against damage by cytokines • Prevent myocardial and pulmonary Reperfusion injury
	Protocatechuic acid	• Protective agent against cardiovascular diseases and neoplasms • Anti-oxidant activity including inhibition of generation as well as scavenging of free radicals and up-regulating enzymes which participate in their neutralization
	Ferulic acid	• Readily forms a resonance stabilized phenoxy radical which accounts for potent anti-oxidant potential
	Gallic acid	• Anti-oxidant
	Caffeic acid	• Anti-oxidant • Anti-cancer
Flavonoids	Rutin	• Anti-allergic

Table Continued

		• Anti-inflammatory • Anti-proliferative • Anti-carcinogenic • Protectors against coronary heart disease, cancers, and inflammatory bowel disease
	Quercetin	• Chemopreventive • Anti-proliferative • Decreased expression of mutant p53 protein and p21-ras oncogene • Induction of cell cycle arrest at the G1 phase • Inhibition of heat shock protein synthesis • Anti-inflammatory and anti-allergy effects mediated through the inhibition of the lipoxygenase and cyclooxygenase pathways, thereby preventing the production of pro-inflammatory mediators
	Epigallocatechin Gallate	• Anti-oxidant • Inhibits cellular oxidation • Prevents free radical damage to cells • Chemopreventive agent
Terpenes	Carnosic acid	• Anti-Infective Agent • Disinfectant • Anti-oxidant
	Rosmarinic acid	• Anti-Inflammatory Agents • Non-Steroidal • Act by blocking the synthesis of prostaglandins by inhibiting cyclooxygenase, which converts arachidonic acid to cyclic endoperoxides, precursors of prostaglandins. • Inhibition of prostaglandin synthesis accounts for their analgesic, antipyretic, and platelet-inhibitory actions • Anti-oxidants • Serine Proteinase Inhibitors
Natural antioxidant	Ascorbic acid	• Reducing agent • Anti-oxidant agent • Fighting bacterial infections, detoxifying reactions, formation of collagen in fibrous tissue, teeth, bones, connective tissue, skin, and capillaries
	Propyl gallate	• Anti-oxidant • protects against oxidation by hydrogen peroxide and oxygen free radicals, • Food additive • radical scavenger

Table Continued

	Resveratrol	• Anti-oxidant • Chemopreventive • Anti-inflammatory • Inhibits cyclooxygenase and hydroperoxidase functions (anti-promotion activity) • Induces promyelocytic leukaemia cell differentiation • Anti-cancer • Anti-viral • Neuroprotective • Anti-aging • Cardioprotective
Volatile Oils	Thymol	• Pharmaceutical preparations • Anti-septic • Anti-bacterial • Anti-fungal
	Eugenol	• Perfumeries • Flavorings • Essential oils • Local antiseptic • Anesthetic
	Menthol	• Flavoring • Local anesthetic • Counter-irritant effect on skin and mucous membranes • Local analgesic • Anesthetic
	Piperine	• Cytochrome P-450 Enzyme Inhibitor

Table 7 Phytochemicals- a potential source of dietary foods and its benefits

Class	Phytochemical Compounds	Dietary Sources	Biological benefits
Carotenoids	Beta-carotene Lycopene Lutein Zeaxanthin	Red, orange and green fruits and vegetables including carrots, cooked tomatoes, leafy greens, sweet potatoes, watermelon	Inhibit cancer cell growth, Work as antioxidants and improve immune response
Flavonoids	Anthocyanins, Quercetin	Apples, citrus fruits, onions, soybeans and soy products coffee, tea	Inhibit inflammation and tumour growth, Aid immunity, Boost production of detoxifying enzymes in the body

Table Continued

Polyphenols	Ellagic acid, Resveratrol	Green tea, grapes, berries, citrus fruits, apples, whole grains, peanuts	Prevent cancer formation, Prevent inflammation, Work as antioxidants
Terpenes	Limonene, Carnosol	Cherries, citrus fruit peel, rosemary	Protect cells from becoming cancerous, Slow cancer cell growth, Strengthen immune function, Limit production of cancer-related hormones, Work as antioxidant

Summary

Phytochemicals have immense potential for the management and treatment of microbial infections and wounds. Anti-microbial, anti-oxidant and wound healing phytochemicals encourage blood clotting, fight infection and accelerate the healing of wounds. Therefore, it is important to study and examine all options available and need to be improved. The phytomedicines are not only cheap and affordable but are safe and less toxic than allopathic drugs. Phytochemicals need to be identified and formulated for treatment and management of infections and wounds. However, there is a need for standardization, safety, and scientific evaluation before recommending phytochemicals for therapeutic purpose.

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Conflict of interest

There is no conflict of interest.

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