

PHYTOCHEMICALS AND THEIR AMELIORATIVE POTENTIAL AGAINST COVID-19

Abstract

There are several chronic ailments around the globe which needs attention of scientific community for the search of possible cure. The traditional medicinal systems are used by the mass, where healthcare system is not prevailed its availability like the remote areas, or tribal populations residing in Islands or forest regions. These medicinal system utilizes herbal formulations rich in bioactive compounds or phytochemicals also commercially available as natural products. In the present chapter, different phytochemicals has been documented following their classifications, ameliorative effects. The preparation methods of these phytochemicals has been discussed. As COVID 19 is emerging continuously in different strains and still needs research besides vaccines for the development of medication for primary treatment, some potent bioactive compounds present in Ayurveda system are also conversed as potential antiviral activities

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I. INTRODUCTION

Phytochemicals are naturally occurring bioactive, chemical compounds derived from plants that have health stimulating, ailments preventive or medicinal properties. They contribute in plants colour, odour and flavour. They are present in our routine food, herbal products, dietary supplements and processed packaged foodstuffs such as multigrain cereals, protein formulations, soups and commercially available natural beverages. They are also marketed in the formula of concentrated pills, capsules, powders and tinctures such as a single vitamin substitute or in combination preparations. The consumption of these phytochemicals has been studied as an effective strategy for reducing genotoxic damage, cardiovascular diseases and cancer (1). Indian cuisine is well known for the use of spices. These spices are studied with enormous health benefits including prevention from deadly ailments including cancer (2). On consumption they chiefly effects the chemical processes inside human bodies in helpful manners. This can be confirmed by the findings from studies conducted all around the world where phytochemicals have proved their potential to boost the immune system, prevent carcinogenesis, avert DNA damage and promotes nucleic acid repair, reduce oxidative stress, trigger apoptosis, hormone regulation and fight several other pathologies (1,2). In a study malnutrition was regarded to have a direct impact on cancer and disorders (3).

A wide range of phytochemicals/Bioactive compounds have been acknowledged so far, and researchers have only initiated to explore their ameliorative effects(4). In past few years, several technological advancements and scientific way of research revolutionized leading to era of advanced computational analytical softwares, genome mining softwares, engineering tools and microbial culturing techniques are answering the need for such encounters and leading to a new era of prospects in scientific world. Consequently, growing interest in usage of natural products as preventive drugs is being fortified, in the tackling of antimicrobial resistance(5). Here, in the present chapter, recent technological developments has been summarized that are creating a new era of natural phytochemicals based medications, along with highlight selected applications in recent epidemic and advices about the key breaks in drug discovery.

Traditionally, phytochemicals derived through different methods, have played a vital role in scientific search of potential cure in naturopathy that has been practised from thousands of years in Asian continent, especially for carcinoma progression and infectious diseases(6) but also for the research in other beneficial areas, such as preventive strategies for cardiovascular ailments (for example, statins) and other conditions of multiple sclerosis (for instance, fingolimod)(7).

These bioactive compounds offer wide range of properties as compared to chemical compounds synthetically synthesized under lab conditions, which possess both advantages and challenges for the research for future drugs. These compounds have vast scaffold range and structural complexity. These bioactive molecules generally possess higher molecular mass, with higher count of specifically sp^3 carbon atoms and oxygen atoms with comparatively lower number of active nitrogen along with similar count of halogen molecules, greater numbers of H-bond acceptors and donors(8). These structural differences in bioactive compounds make them profitable; for instance, the higher structural rigidity of phytochemicals showed promising outcomes studied in protein-protein interactions that can lead to a breakthrough in drug discovery mainly targeting protein-protein interaction.(9)

There is a whole list of the phytochemicals classes (Table 1) which now days became a matter of scientific interest, including identification of food sources and research potential benefits mentioned thousands years back in traditional medicinal system in Asia Pacific region (Table2).There is increase in use of phytochemicals in chemoprevention and chemotherapy has been observed in research of past decade (1).

The phytochemicals/bioactive compounds/ Natural signaling pathway principally acts through modulation of cell signaling pathways in case of anti inflammatory or immunoregulatory effects, while in case of oxidative stress, the antioxidants presents come into rescue. Due to emergence of COVID 19, these phytochemicals are also being explored for antiviral activities.

Table 1: Different Classes of Phytochemicals/Natural Products

Phytochemicals classes	Food Source	Possible Health Benefits
Carotenoids (beta-carotene, lycopene, lutein, zeaxanthin)	Red, orange and green fruits and vegetables including broccoli, carrots, cooked tomatoes, leafy greens, sweet potatoes, winter squash, apricots, cantaloupe, oranges and watermelon	Inhibition of skin cancer cell progression, acts as antioxidants and promotes immune response (11)
Flavonoids (anthocyanins and quercetin)	Apples, citrus fruits, onions, soybeans and soy products (tofu, soy milk, edamame, etc.), coffee and tea	Anti-inflammatory, anti-tumor , antioxidative (12)
Indoles and Glucosinolates (sulforaphane)	Cruciferous vegetables (broccoli, cabbage, kale, cauliflower and Brussels sprouts)	Promoting detoxification and process of carcinogens, hormone regulation, block carcinogens (13)
Inositol (phytic acid)	Bran from corn, oats, rice, rye and wheat, nuts, soybeans and soy products (tofu, soy milk, etc.)	Prevention of carcinoma metastasis, metal toxicity(14)
Isoflavones (daidzein and genistein)	Soybeans and soy products (tofu, soy milk, edamame, etc.)	Prevent tumor progression, hormones regulation and antioxidant, liver toxicity(15)
Isothiocyanates	Cruciferous green leafy vegetables (broccoli, cabbage, collard greens, kale, cauliflower and Brussels sprouts)	Induction of inhibition metabolic process of carcinogens, cease tumor growth and acts as, Antioxidantive agents (16)
Polyphenols (ellagic acid, eugenol, anethole and resveratrol)	Green tea, grapes, wine, berries, citrus fruits, apples, whole grains, spices and peanuts	Prevent cancer progression, anti inflammatory effects and work as antioxidants (17)

Terpenes (perillyl alcohol, limonene, carnosol)	Cherries, citrus fruit peel(orange,lemons), rosemary	Prevent metastasis, prevent inflammation and acts as antioxidants (18)
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Table 2: Phytochemicals used in Traditional Indian and Chinese Medicinal System

Phytochemical	Source	Protective effects
Acetyl- α/β -boswellic acid (α/β -ABA),	<i>Boswellia sacra</i> Flückiger- Dupiron (Bursaceae)	Anticarcinogenic, antioxidative (19)
Artesunate (hemisuccinate form artemisinin)	<i>Artemisia annua</i> L. (Asteraceae)	Anti inflammatory, anti tumor, antimicrobial (20)
Baicalein (5,6,7- trihydroxy-2phenyl-4H-1- benzopyran-4-one)	<i>Scutellariabaicalensis</i> Georgi (Lamiaceae).	Anti-inflammatory , anticarcinogenic(21)
Baicalin (5,6,7-trihydroxy- 2-phenyl-4H-1- benzopyran-4-one 5,6- dihydroxy-4-oxo-2phenyl- 4H-1-benzopyran-7-yl- β - d-glucopyranosiduronic acid, C ₂₁ H ₁₈ O ₁₁)	Glucuronide derivative of baicalein	Anticarcinogenic,anti- inflammatory (22)
Berberine (isoquinoline alkaloid)	<i>Coptis chinensis</i> also known as Frenchrhizome (Ranunculaceae), fund in barberry roots and other source Oregon grape root.	Gastroentertitis,anti- inflammatory(23)
Borneol	<i>Acorus calamus</i> L. (Acoraceae)	Anti inflammatory, antiapoptotic(24)
Chlorogenic acid(polyphenol)	Green coffee beans, cocoa,	Anticarcinogenic,anti- inflammatory (25)
Carvacrol	<i>Origanum vulgare</i> Linn. (Lamiaceae)	Antioxidant, anti- inflammatory (26)
Curcumin	<i>Curcuma longa</i> L. (Zingiberaceae)	Anticancerous, antioxidant, antiinflammatory(27)
Dihydrokaempferol (DHK)	<i>Bauhinia championii</i> (Benth.) Benth. (Fabaceae)	Anti-inflammatory, antioxidant(28)
Ellagic acid	Fruits and vegetables	Anticancerous, antioxidant and anti apoptotic(29)
Isoliquiritigenin (ISL)	Soyabeans,licorice,and shallots	Antioxidative, anti inflammatory(30)
Oxymatrine (alkaloid)	<i>Sophora alopecuroides</i> L. (Fabaceae)	Immunosupressent and anti-inflammatory(31)
Quercetin (3,3',4',5,7- pentahydroxyflavone),	Fruits and vegetables	Anticancerous, anti- inflammatory(32)
Rutin (quercetin-3- rhamnoglucoside	Citrus fruits	Antioxidant, anti- inflammatory(33)

Saikosaponins	Radix Bupleuri, <i>Bupleurum chinense</i> DC. (Apiaceae)	Antioxidant, anti-inflammatory, anti-cancerous(34)
Tanshinone IIA (TSA)	<i>Salvia miltiorrhiza</i> Bunge (Lamiaceae)	Anti-inflammatory, anticancerous(35)
Tetramethyl pyrazine/ligustrazine	<i>Oreocome striata</i>	Anti inflammatory, anti carcinogenic(36)
Visnagin/furanocoumarin derivative	<i>Ammi visnaga</i> (L.) Lam. (Apiaceae)	Antioxidant, anti-inflammatory, anti carcinogenic (37)
Withaferin A	<i>Withaniasomnifera</i> (L.) Dun. (Solanaceae)	Anti-inflammatory, antioxidant (38)

II. PRACTICES USED FOR PHYTOCHEMICALS ABSTRACTION, ISOLATION, AND PURIFICATION ANALYSIS

1. Abstraction of Phytochemicals Using Different Solvents: There are several classes of phytochemicals, which becomes the basis of identification of different methods for isolation of different classes of phytochemicals. In solvent based process polarity is primarily considered (like dissolves like), followed by stability of the properties, for instances phenolic compounds has antioxidant properties, in case of walnut methanol is more effective solvent then ethanol (39). A suitable solvent with comparable polarity to the solute will aid the appropriate dissolution of the solute. The polarity of the solvents varies, from slightest polar to greatest polar, the most widely used solvents used as follows: Hexane < Chloroform < Ethylacetate < Acetone < Methanol < Water. Plant extracts are usually prepared and then stored In dry powdered forms, which later used for further analysis.

For the preparation of plant extracts different plant parts are used such as roots, shoots, fruits, leaf and stem (figure 1 and 2). After proper washing and sterilization, dried and homogenized for further processing, before selecting the plant of interest, a vast knowledge about its status must be considered as endangered species are prohibited for such methods, along with it in case of some particular plants, permission of certain organizations is mandatory as some are part of aesthetic beliefs. The agenda of the phytochemical research is to find appropriate, sensitive and fast techniques that can easily screen the source material along with identification of their ameliorative properties such as antioxidative, antibacterial, or cytotoxic, collectively (40).

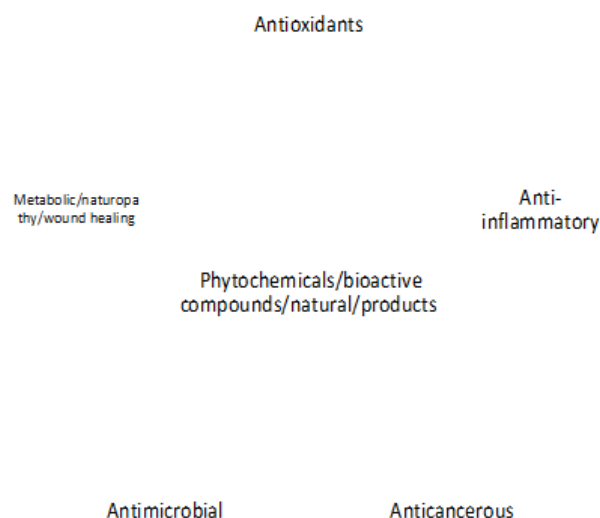


Figure 1: Phytochemicals Well Acknowledged Effects

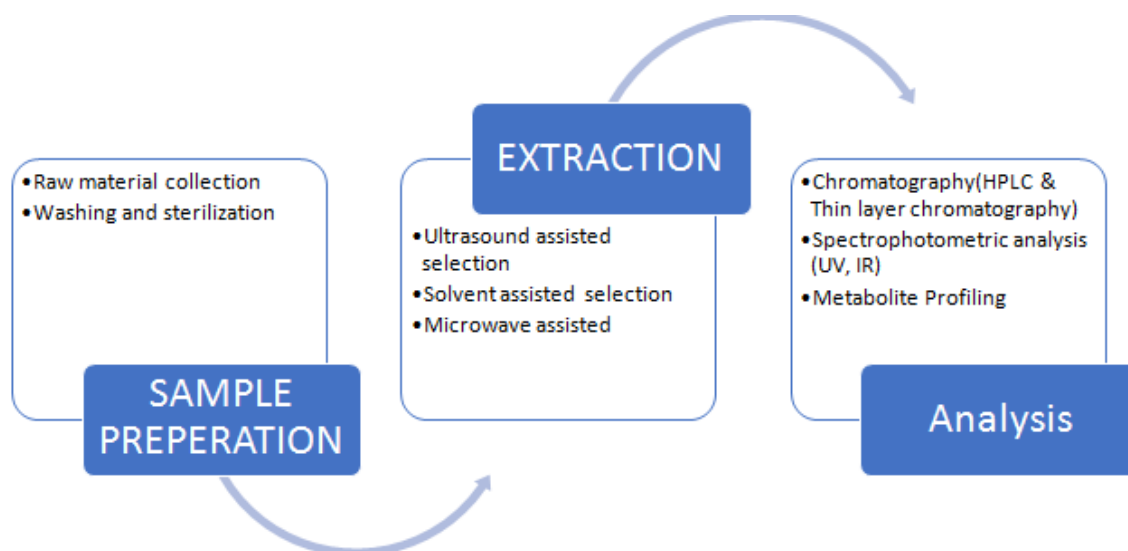


Figure 2: Preparation of Phytochemicals/ Bioactive Compounds Formulations

2. **Microwave-Assisted Extraction (MAE):** This method of extraction involves usage of electromagnetic radiation (300 MHz to 300 GHz) consisting of both electric and magnetic fields for isolation of phytochemicals from various plant parts of fruits and vegetables . These waves of electromagnetic nature comprises of balanced combination of both electrical and a magnetic field. These are designated as two perpendicular fields. The advanced methods are identified which in lesser extraction time prevents the loss of natural antioxidant properties such as stability and also use less amount of solvent(41). There are some factors which affects the effectiveness of the microwave extraction method such as process appropriate conditions including, specific temperature, balanced solvent composition, and time taken for completion of process extraction.
3. **Ultrasonic-Assisted Extraction(UAE):** It has been among one of the widely used methods used in the preparation of plant extract compounds from raw materials (43).

Ultrasound waves are utilized for the disruption of plant cell walls in a homogenized plant sample with suitable solvent (ultrasonic bath) with controlled temperature and time which leads to increase in the ability of the solvent's to cross the cells and results in a greater extraction yield. The drawback of the method is lower yield besides this it is a green/clean technology that also protects the environment from production of toxic substances Tabaraki *et al.* (44).

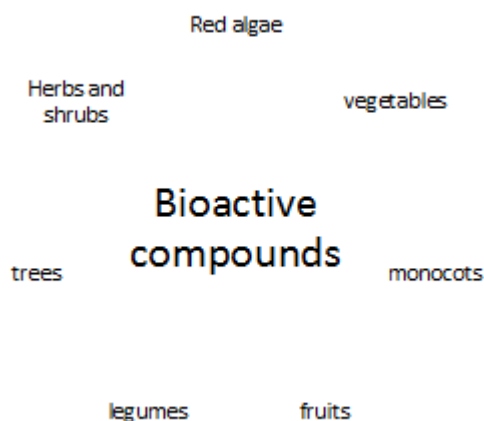


Figure 3: Different Sources of Bioactive Compounds

4. Methods used for Isolation and Purification of Bioactive Molecules from Plants

Extracts: The process of isolating pure form of phytochemicals from plant extracts is a dynamic process that has revolutionized with new development in past decade (45). These modern methods lead to development of several bioassays for extraction, separation, and purification for pure formulation preparation (figure3).

There are some factors that should be considered during isolation and purification methods as sometimes they hinder the separation process of bioactive compounds such as the plant part used for extraction as few parts has number of debris and toxic chemicals as well for instance usage of seeds for bioactive compounds isolation as these naturally consists of certain inhibitors used by plants as defense mechanisms (46). Different solvents are used to prepare different formulations of bioactive/phytochemicals compounds based on functional chemical and physical properties. Generally chromatography methods are widely used for the isolation of bioactive compounds along with ease in purification at later stages. Different types of chromatography techniques used for bioactive compounds separation including HPLC (High Pressure Liquid Chromatography), which is technically advanced instrument which fastens the purification process with high accuracy.

In the era of new developed scientific instruments such as chromatography(HPLC), electrophoresis and spectrophotometry leads to a several times acceleration in the process of isolation and identifications of the bioactive molecule of interest. A wide range of different variations of spectroscopic techniques are available nowadays such as UV-visible, Infrared Red (IR), Nuclear Magnetic

Resonance (NMR), and mass spectroscopy can easily and accurately identify the composition(47).

- 5. Purification of the Active Bioactive Molecules from Crude Extract:** The prepared plant extracts contains several bioactive molecules which further processed for the preparation of commercial nutraceuticals in the form of serums, tablets and other powder forms. Paper thin-layer and column chromatographic methods are used widely used because of their ease to use, economically and availability of wide range of solvents and stationary phase(48) Mostly Silica powder, alumina, cellulose, and polyamide materials are utilized for the separation process for identification of specific bioactive compound from the combination phytochemicals present in the crude extract(44). After the isolation, identification of the bioactive compound structure is must to analyse its further usage

III. STRUCTURAL IDENTIFICATION OF THE BIOACTIVE MOLECULES

As the crude plant extracts contains several bioactive compounds along with debris which is after purification step removed, with a filtrate remaining with bioactive compounds. The filtrate further processing involves identification of constituents for the identification of targeted bioactive compound different spectroscopic methods are utilized including Ultraviolet-visible, Infrared (IR), Nuclear Magnetic Resonance method (NMR), and variations of mass spectroscopy. The basic principle of spectroscopy techniques the concentration of absorbed electromagnetic radiation by the different organic particles present that produces different spectra on the basis of its structure (bonds of the molecule), based on the spectra different constituting chemical compounds are identified. Based on the structure of different phytochemicals different spectroscopies are used

- 1. Ultraviolet(UV)-Visible Spectroscopy Variation:** Ultraviolet-visible spectroscopy is one of the most widely used techniques for the aromatic molecules present in purified plant extracts as they served as dominant chromophores absorbing the UV range effectively(49). The natural phenolic compounds including different classes of anthocyanins, tannins, polymer dyes, and phenols, form sturdybond complexes with iron molecules can be recognized through ultraviolet/visible (UV-Vis) spectroscopy (34). Moreover, it also provides information about the total phenolic contents in a short time period with high sensitivity(50)
- 2. Infrared Spectroscopy(IR) Method:** Besides identification of phenolic contents, structure identification is must for further replication and commercial production of the phytochemicals which is possible through IR spectroscopy which based on the principal of vibrational changes caused by the different bonds present in the bioactive compounds with different bondings have different vibrational frequencies on the basis of bond constitutions(51). Fourier Transform Infrared Spectroscopy (FTIR) is one of the widely used method with a high-resolution for the identification of the compounds/chemical constituents and also identify the structural aspects of the compound of interest. It is prompt and non-destructive method to identify the formulations of herbal products sold as extracts or in powder formulations.

- 3. Nuclear Magnetic Resonance Spectroscopy (NMR) Technique:** NMR method is principally related to the usage of magnetic properties of the molecule nuclei that enabled to identify the active biomolecules by identifying the variances present between the several magnetic nuclei of different bioactive compounds in a mixture, and thereby providing a distinct image of nuclei positions with demonstration of atoms are present in compound.(52)
- 4. Mass Spectrometry (MS):** The bioactive molecules identified from crude extract were isolated and purified by chromatography and identification through spectroscopy which provides (53) a fast, sensitive and precise identification of phytochemicals/nutraceutical compounds present in medicinal herbs formulations, specifically in case where a pure standard form is difficult to obtain from complex(54). Another combination of Liquid chromatography and MS has been extensively utilized for the exploration studies of bioactive phenolic compounds.

IV. COVID 19 AND BIOACTIVE COMPOUNDS

Since the emergence of first occurrence of COVID 19 case in November 2019, in China, where it caused respiratory infection, the disease (Corona Virus or COVID-19) blow-out worldwide as a nightmare pandemic across the globe and still continuing through emergence of new variants. As a result, vaccine development became a prime target which is successfully implemented as well. However, the fear is still there as it is still affecting people through modulating its forms and appearing with different forms including the Omicron sub-variants such as BA.2 and BA.2.38 in Asia (India), while the BA.4 and BA.5 sub variants are also observed in other parts of the world. Moreover, countries with lower economies with poor healthcare system are still suffering for the access of primary treatments(51). Therefore, along with addition to the present medication and preventive system treatment approaches, there is a prerequisite of long-term immune system heightening strategies to combat future pandemics. In this perspective, the ancient Ayurvedic or Unani or Chinese traditional medications can play a significant role in search of an unconventional method for COVID-19 treatment. The phytochemicals or Bioactive compounds present in traditional herbs still serving as a treatment for 80% of the world's population for their common health issues and severe ailments as well.(56) These high potential herbs with thousands of bioactive compounds is well recognized and acknowledged by China during the initial days of COVID-19 (56). Lianhuaqing wen and ShufengJiedu). Asian countries like China, India, and South Korea showed significantly lower mortality rate in COVID cases because of their issued guidelines for their nationals for the usage of traditional and herbal medications in initial days(57)

Several bioactive molecules, chiefly the secondary metabolites, were studied recently for the prevention of COVID-19 and SARS-CoV-2 preventive potential. Among the different categories of reported high potential phytochemicals with high inhibitory activity for COVID-19 infection consists three major groups of phytochemicals consisting of secondary metabolites three main classes including terpenoids, alkaloids, and phenolics (Figure3)

- 1. Terpanoids:** Terpenes and its derivatives are considered as the major group of phytochemicals (plant secondary metabolites viz soperene (C_5H_8) derivatives), which are synthesized through the isoprenoid or the mevalonate pathway with Acetyl-CoA precursor. There are different classes of terpene (hemiterpenes, monoterpenes,

sesquiterpenes, diterpenes, sesterterpenes, triterpenes, tetraterpenes, and polyterpenes) differentiate on the basis of presence of quantity of isoprene units present in the structure. These have great significance and therapeutic usage against several ailments(60). For instance, Diterpenoids, isolated from *Torreya nucifera* and Ferruginol showed potential inhibition against Covid 19, where as the terpenoid derivative 22-hydroxyhopan-3-one and 6-oxoisoguesterin along with (10-hydroxyusambarensine, cryptoquinoline) were showed strong protective effect against SARS-CoV-2 (61). Tanshinones are diterpenes *Salvia miltiorrhiza* (62). **Saponins isolated** the different parts of the plant *Aesculus turbinata* that has been widely utilized as herbal medications and products, with ameliorative properties (EC_{50} 6.0 μ M) (63). **Withanone derived from *Withania somnifera*** (Ashwagandha), also showed promising effects against Covid19 in molecular docking (64).

Alkaloids are metabolically active, cyclic compounds with well acknowledged therapeutic, nutritional, toxicological, potential which leads to the several studies to find their effects against Covid 19(60). For instance, Cepharanthine(tetrandrine) derived from plant *Stephania tetrandra* showed significant effect against the SARS-CoV-2 NSP12-NSP8 (65).

Phenolics, a abundant plant secondary metabolites group (8000) found around the globe that made its research for therapeutic potential for Covid. These are phenylalanine derivatives which are produced through the metabolic pathway of phenylpropanoid synthesis. They comprises of different bioactive compounds containing classes of phenols, phenolic acids, hydroxycinnamic acids, phenylacetic acids, phenylpropenes, quinones, coumarins, stilbenes, lignans, xanthones, neolignans, tannins, melanins, and flavonoids (61). There is number of phenolic constituents studied for their ameliorative potential against COVID-19 (figure4).

There is a long list of different bioactive compounds among the above mentioned list of terpenoids, alkaloids, and phenolics which can be identified as strong prospective medication for COVID-19 and its variants(figure 5).

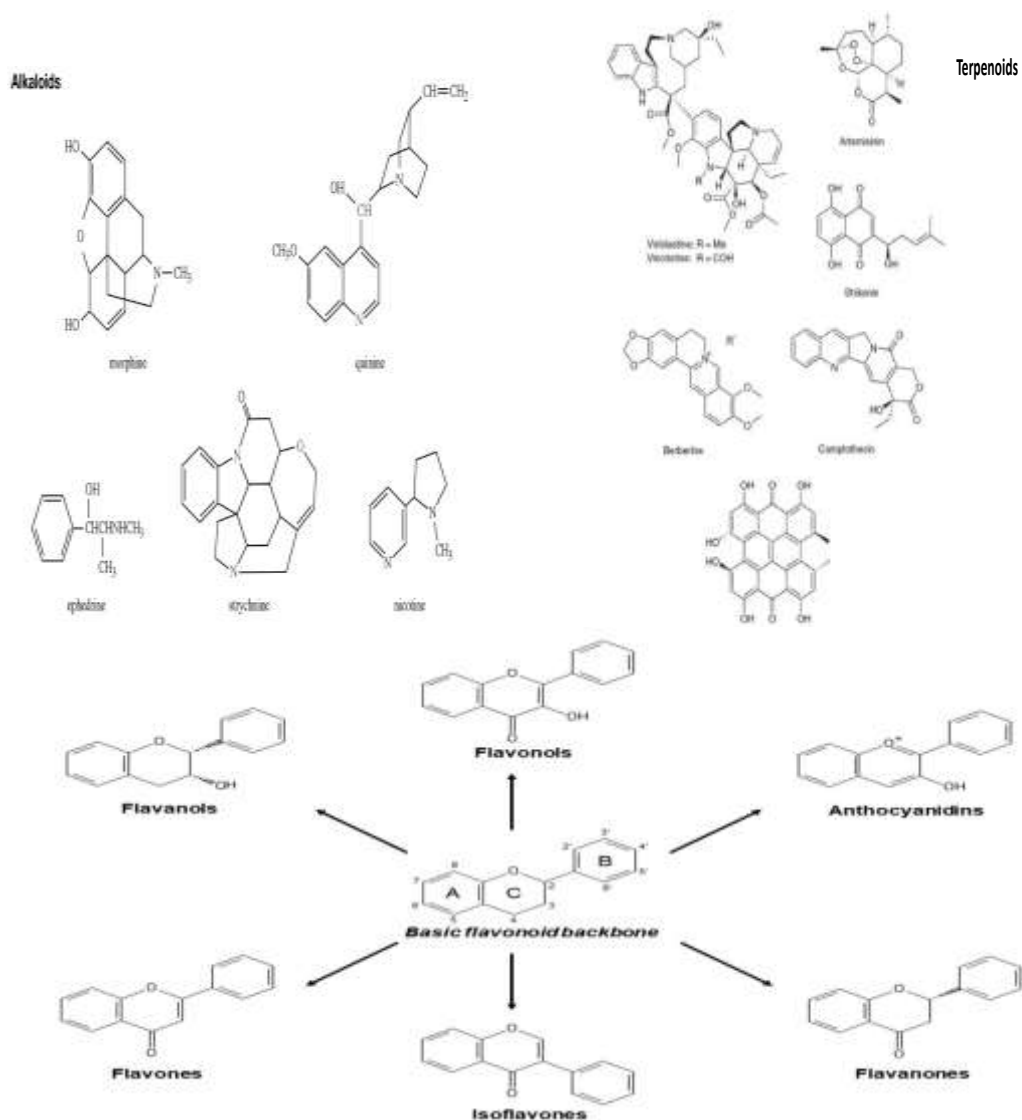


Figure 4: Structure of Different Bioactive Compounds Structure

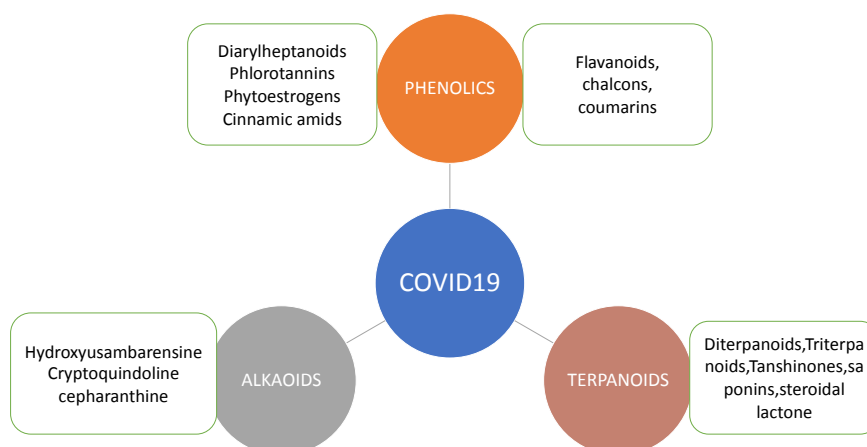


Figure 5: Phytochemicals/Bioactive Compounds with Ameliorative Potential Against COVID 19

V. COMMONLY USED INDIAN PLANTS WITH AMELIORATIVE POTENTIAL AGAINST COVID 19

Indian Ayurveda system is one of the worlds well acknowledged ancient medicinal system, consisting of remedies against chronic ailments. These remedies often consist of combination of different plant extracts enriched in bioactive compounds, the plants utilized in preparing the plant extracts also been utilized in every Indian household routine food preparation and around the globe in some traditional medicinal practices. This also explains contribution of diet in the lower mortality rate during Covid wave observed in Asian Continent as compared to rest of the world, with high health infrastructure. There are some herbs which came into limelight during pandemic and research is still continued for their therapeutic potential

- 1. *Allium Sativum L. (Garlic):*** *A. sativum* or Garlic is one of the famous ingredient of common Indian households and also known for its pungent smell, it contains diverse range of bioactive chemicals, mainly includes allicin and its derivatives, including alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, with other compounds such as ajoene, and S-allyl-cysteine. In traditional medicine garlic oil is used for muscular pains, arthritis and raw garlic for boosting metabolism, as it also generates heart burn in excess consumption its consumed in the form of pickles during winter and usage decreases during summers. There is number studies has been conducted to study the ameliorative properties of garlic extract, it showed promising results by decreasing levels of serum proteins(TNF- α , ICAM-1 and immunoglobulins(IgG & IgM)), thus proven role in enhancing immunity(66). Thus, emergence of new strains of Covid 19 scientist also began to study garlic antiviral properties, explored earlier , for instance aqueous garlic extract found to be preventive against the pathogenic Newcastle disease virus studied in embryonated chicken eggs, pretreated with aqueous garlic extract preparation (67). In another study, conducted by Rasool *et al.*, (68,) *A. sativum* also found effective against avian influenza virus H₉N₂ on Vero cells (69). Its also studied as immunobooster in *in vivo* studies conducted in mice model, showed substantial decrease in count of inflammatory cells, eosinophils infiltration along with fall in levels of serum IgE(70).
- 2. *Cinnamomum Verum J.Presl. (Cinnamon) or Cinnamomum Zeylanicum:*** Blume Cinnamon or commonly known as dalchini in Indian households, is a major constituent of desserts as well as savoury dishes to enhance flavour, in Ayurveda system it is either consumed in powder form(generally mixed with other herbs) or in the form of water extract for the treatment of digestive, respiratory and circulatory system related ailments. It is also used in case of joints pains, also nowadays for the obesity treatments (71). The major bioactive compounds present includes mainly the cinnamaldehyde devarients along with minor constituents including eugenol, camphor, and cadinene, the plant extracts commonly prepared for herbal medications involves prime usage of cinnamon barks along with, leaf, root, and fruit, respectively on the basis of its target ailment. The bark extract showed immunomodulatory effects by increasing the levels of serum immunoglobulins in case of inflammation(72), Similarly in another study conducted by Joshi *et al.*, (73) alcoholic preparation of cinnamon bark powder found to suppress the TNF- α and leucocyte count *in vivo*. The well acknowledged immunomodulatory effects makes it's a potential candidate for antiviral properties as well studied against Newcastle virus in chickens, the oil and powder extract of cinnamon exhibited immunostimulatory

effects against the virus, In another study it is also found effective(74) against the H1N1 and HSV1 virus strains by significantly decreasing the virus infectivity (75).

The bark extract preparation of Cinammon showed its immunomodulatory potential through significantly increasing the quantity of serum immunoglobulins levels, phagocytic index, neutrophil adhesion, and antibody titer. The bioactive molecules procyanidine polyphenols (Type A), studied in *C. zeylanicum* bark extract exhibited high anti-inflammatory potential against edema induced by carcinogens (76). Another study also confirmed the immunomodulatory potential of Cinnamon alcoholic plant extract prepared using its bark through significantly suppressing the intracellular release of TNF- α (murine neutrophils) dynamics and leukocytes number (pleural fluid) as well as hindering the expression of TNF- α gene countenance in lipopolysaccharide-stimulated human peripheral blood mononuclear cells (77).

3. ***Curcuma Longa L. (Turmeric):*** *Curcuma longa* l. or turmeric/haldi is being utilized in Indian cuisine as natural food colour, but also as a common immune boosting drink (Turmeric milk, also gaining popularity in western world as Turmeric Latte). Turmeric powder has been also used in covering minor cuts and injuries from the ancient time. The chief bioactive compound found in Turmeric is Curcumin, which is categorized under group of phenolic compounds known as curcuminoids, about hundred types of curcuminoids has been isolated and studied, out of which more than half present in turmeric alone. The plant extract of turmeric in various studies showed antiallergic effects, by significantly reducing the concentrations of IgE, IgG1, mMCP-1 and Th2 proteins in serum thus showing its immunomodulatory potential(78). There are number of studies available proving the anti-inflammatory potential of *C. longa* either alone or in synergistic formulations (79). In case of antiviral effects, the aqueous extract found to be protective against dengue virus both *in vivo* and *in vitro*(80). Another study conducted by sornpet *et al.*, water and alcoholic(ethanol) crude extracts preparations of turmeric showed positive outcomes against H5N1 through upregulating TNF- α and IFN- β mRNA expression, by inhibiting viral replication (81).
4. ***Linum usitatissimum L. (Flax Seed):*** Flaxseed (*Linum usitatissimum* L.) or Alsi, has gained worldwide acknowledgment in past decade as a healthy food found beneficial in weight loss dietary programs because of its nutritional richness and high fibre content, thus it is a high potential source enriched with bioactive compounds. The phenolic group of compounds present in flax seed showed immunomodulatory effects through significant decrease in T cells thus modulating the cell mediated immune response in studies *in vivo* (81). The hetropolysacchrides present in flax seed showed antiviral activity by inhibiting expression of viral antigen and also inhibiting viral replication (82).
5. ***Nigella Sativa L. (Black Cumin):*** *Nigella Sativa's* commonly known as black cumin or jeera, is also a prominent ingredient of Indian food preparations. It is consumed raw or in powder dry roasted form for digestive disorders in Ayurveda, nowadays it is also an ingredient of commercial herbal formulations. The main chemical composition includes different bioactive compounds present in cumin are thymoquinone, dithymoquinone, and dihydrothymoquinone. Among these, thymoquinone is the major bioactive compound. The alcohol extract of cumin seeds showed immunomodulatory effects by affecting the lymphocytes proliferation(83). The oil extract of cumin seeds has been found to exhibit anticarcinogenic effects studied *in vitro* in human alveolar basal epithelial A549 cell line

(84). There are number of molecular docking studies conducted which observed the significant antiviral potential of bioactive compounds present in crude cumin extract(85).

6. ***Ocimum Sanctum L. (Tulsi)***: *Ocimum Sanctum* which is popularly known as holy basil or Tulsi that has deeper aesthetic value, it is worshipped in Hindu religion. The usage of tulsileafs or droplets of tulsi extract (modern formulation) is a popular common household treatment in India for cold and cough. There are several bioactive compound present in ocimum sanctum extract including, different concentrations of phytochemicals consisting oleanolic acid, rosmarinic acid, ursolic acid eugenol derivatives, along with other compounds such as linalool, carvacrol, β elemene derivative, β caryophyllene, and germacrene. The extract of O.sanctum has been studied *invitro* in HL-60 cells, where it showed significant decrease in inflammation of lung cells (85). In another study, Bhalla *et al.*, observed immunomodulatory potential of leaf extract with reduction in number of infected liver cells with heightened immune response(86). The antiviral properties of *Ocimum sanctum* extract has been studied in H9N2 viruses, where significant reduction of viral multiplication was observed.
7. ***Phyllanthus emblica L. (Amla)***: *Phyllanthus emblica L* or Amla or Indian gooseberry is a rich source of antioxidants, and advertised constituent of many skin, hair care products and toothpaste. It is bitter in taste when consumed raw but tastes sweeter afterwards due to reaction with salivary amylase. It is also known for high content of vitamin C. The quantification study through HPLC, the major bioactive compounds recognized includes high concentration of gallic acid, along with traces of ascorbic acid, minor amounts of ellagic acid, rutin, quercetin, and catechol. The plant extract has been reported as antitoxic agent against chromium induced genotoxicity in lymphocytes by significantly increasing levels of of IL-2 and INF γ (88). It also showed immunostimulatory effects by proliferating splenocytes, reducing inflammation(85). Amla extract in a study by Xiang *et al.* showed significant, antiviral potential against HSV virus, by preventing viral penetration and replication by inhibiting gene expression of virus(86).

VI. CONCLUSION

Medicinal plants and their therapeutical potential has been recognized as ‘traditional medicine’ and still being used as potential remedies for several health issues in countries with low economy. Highly populated countries still recommend traditional medication as a primary method In areas where is lack of health care infrastructure. Due to the structure complexibility of bioactive compounds, they exhibits enormous health benefits, with high ameliorative potential of plant-derived metabolites or bioactive compounds or natural products are gaining recognition among the scientific community. Besides, vaccine development, the preventive potential of these natural bioactive products may revolutionized the traditional medication development strategies against new emerging strains of SARS-CoV-2, which can be easily available in native countries for a fast, economical and reliable treatments.

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