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Title:	**Therapeutic Potential of Phytocompounds in Medicinal Plants: A Comprehensive Overview in Treating Diseases**
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Therapeutic Potential of Phytocompounds in Medicinal Plants: A Comprehensive Overview in Treating Diseases

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ABSTRACT

Background. Nature acts as a source of abundant bioactive compounds. These compounds hold enormous potential for use in medicine, and phytocompounds are of significance here. They consist of primary and secondary plant metabolites, which are found in different parts of the plants and have a considerable influence on human well-being. They may be phenols, alkaloids, tannins, saponins, flavonoids, glycosides, and steroids. Furthermore, these have promising effects to inhibit, treat, and cure numerous diseases when used naturally or synthetically.

Methods. This review covered almost all different classes of phytocompounds with their potential activities (i.e., antioxidants, anti-inflammatory, anti-aging, anti-cancer, anti-diabetic, anti-allergic, neuroprotective, cardio-protective, hepato-protective, renal-protective, and immunomodulatory) according to their benefits and targeted pathways. Moreover, the study also described some combination therapies of different phytocompounds. These strategies enhance the working capability of phytocompounds and help to provide a strong shield against various life-threating diseases.

Conclusion. The review provided a comprehensive information about phytocompounds and their therapeutic effectiveness. Moreover, it may serve as a starting point to discover or develop new and novel drugs in order to cure various ailments in future.

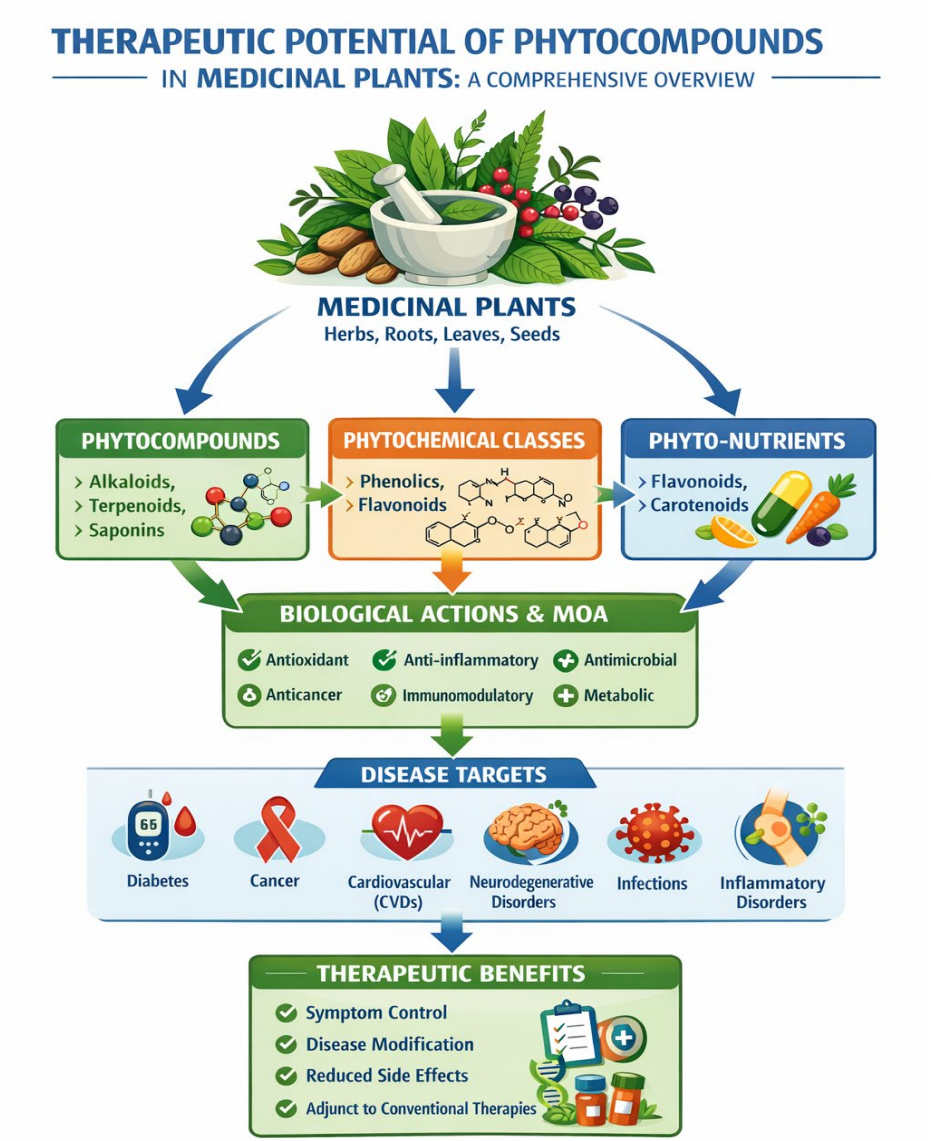
Keywords: anti-aging, anti-diabetic, anti-inflammatory, hepato-protective, immunomodulatory Neuroprotective

Highlights

- The current study aimed to cover innumerable phytocompounds separately and in combined form according to their health-promising effects in different diseases with their mechanism of action and targeted pathways.
- Phytocompounds have gained considerable importance in the pharmaceutical industry due to their efficacy, safety, unique properties, and modes of action.
- Phytocompounds are rather specific and act on associated targets but some may be destroyed due to first-pass metabolism.
- This review helped develop new strategies.
- Combination therapies for different phytocompounds might be the best and distinctive

solution to this problem. This is because one phytocompound can mask the side effect (s) of another, and combination of different phytocompounds may increase health benefits.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Phytocompounds are the bioactive components of plants. These are present in different parts of a plant (i.e., stem, root, seed, leaves, bark, and flowers) and

perform different types of functions, such as color, aroma, flavor, and protection [1]. Nowadays, these naturally-occurring compounds are used for numerous medicinal purposes. These may be cardio-protective, hepato-protective, renal-protective, neuro-protective, anti-cancer, anti-diabetic, and anti-aging. Researchers benefit from these phytocompounds synthetically or naturally to inhibit, suppress, and treat diseases for the betterment of mankind [2]. Many phytocompounds have been prescribed on the basis of their purposes. Dietary phytocompounds are found in different vegetables, fruits, and herbs [1]. Phytocompounds may be primary metabolites, such as sugars, amino acids, proteins, nucleic acid, and chlorophylls. Apart from this, these may be secondary metabolites, such as phenolics, alkaloids, terpenoids, carotenoids, flavonoids, tannins, curcumins, saponins, and glucosides. Secondary metabolites are used therapeutically in the prevention of different diseases [3]. The antioxidant property of phenolic and flavonoid compounds helps control free radical mediated diseases, which protects human body from reactive oxygen species. Phenolics and flavonoids are present in tea and coffee, and other fruit drinks possess high anti-inflammatory, anti-microbial, anti-aging, and anti-tumor activity [4]. Glycosides may be α-glycosides or β-glycosides and are involved in the maintenance of cardiac function, immune function, and neuroprotection [5]. Alkaloids are globally important with their anti-tumor, antimicrobial, and anti-inflammatory activities. Tannins are mostly found in fruits and promote human health by decreasing the possible inhibition of chronic diseases. Saponins are involved in the production of antibodies as an immune-adjuvant, which is the most prominent activity of saponins [6].

Previous *in vitro* studies have suggested that phytocompounds may affect the key cellular pathways associated with oxidative stress and apoptosis, as seen in the current data. In comparison to previous *in vivo* and clinical studies, the current data both supported the previous studies and added new evidences. Several previous studies evaluating plant-based compounds have demonstrated similar patterns of improvement and disease modulation based on biomarker analysis, thereby confirming that these actions are predominant across different experimental systems [3]. The differences between the current and prior studies were primarily in the degree of change, which can likely be attributed to differences in dosage, formulation, length of exposure, and patient demographics. Different diseases are linked with each other, for instance inflammation may be a risk factor for various types of cancers [7]. The combination of different phytocompounds enhances the capability of their work and helps treat deadly diseases more effectively. As an instance, resveratrol also works through mechanisms associated with oxidative stress, apoptosis, and mitochondrial activity. Epigallocatechin gallate has demonstrated synergy in anti-cancer therapy by working in combination with other chemotherapy drugs through increasing apoptosis and suppressing tumor growth [5]. Such multi-target interactions have made phytochemicals a viable option for treating complex ailments including cancer, diabetes, heart diseases, and neurodegeneration. Nowadays, many herbal preparations are also available in the form of ointments, tablets, suspensions, and capsules to treat infections, inflammations, and other chronic diseases more effectively. Research and development of new therapeutic medicines with phytocompounds is hard and expensive [2].

The purpose of this review was to help

researchers get information about already-used and reported phytocompounds easily and quickly. About 300 review articles and 400 research papers were studied. Additionally, search engines, such as Google Scholar, Scopus, Science Direct, ProQuest, Karger, and Molecule were used to conduct this review on the phyto-chemistry and pharmacological use of medicinal plants. This review assisted in filling the gap on those sites where there was a need to develop new strategies. The study covers innumerable phytocompounds separately and in combined according to their health promising effects in different diseases with their mechanism of action and targeted pathways. Many classes include many phytocompounds, their origin and role accordingly.

2. METHODOLOGY

2.1. Literature Search Strategy

Available literature on phytocompounds with medicinal, therapeutic, and herbal applications was obtained through a systematic review of all major academic databases (PubMed, Web of Science, Scopus, and Google Scholar) to ensure that it collected the most comprehensive database of published research. All of the academic databases were chosen based on large repository of published scientific and peer-reviewed biomedical journal articles. Multiple keywords were used to conduct a search [5]. The analytical keywords included: "phytocompounds," "herbal," "medicinal potential," "phytochemicals," "anti-cancer," "neuroprotective," "anti-hepatic," "anti-diabetic," "anti-inflammatory," "therapeutic potential," "nanoparticles," and "bioavailability." The search results for possible treatments or applications of phytocompounds and their potential purposes were based on search terms and various combinations of search terms.

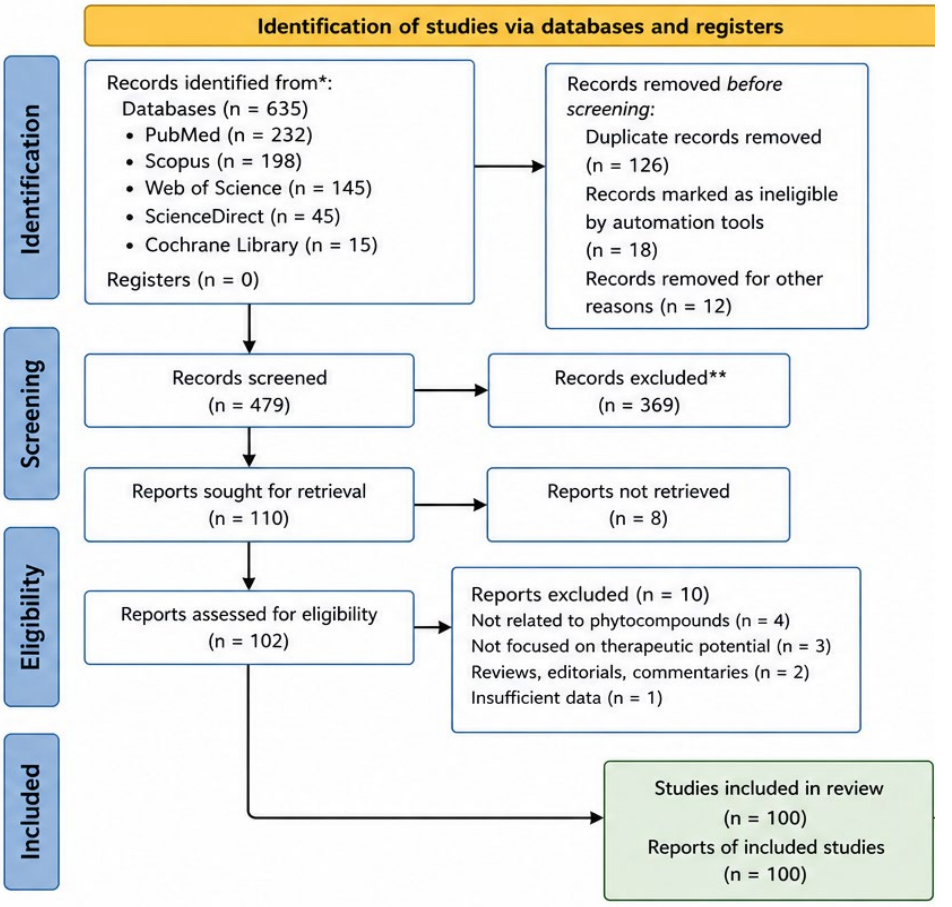
2.2. Data Extraction and Synthesis

Certain inclusion and exclusion criteria needed to be developed to make the research meaningful and credible. Inclusion criteria were based on articles written in English about the use of phytochemicals to treat different diseases. The research articles, clinical trials, reviews, and meta-analyses consisting of mechanisms, effectiveness, and safety of the treatment were chosen. To ensure a high level of research, articles published in reputable journals (Nature, PLOS One, Springer) were chosen. Opinion articles, conference abstracts, articles not in English, and those without peer reviews were excluded from the analysis. Initially, a large volume of records were identified through the initial search, and these records were screened for relevance by means of reading the titles and abstracts. Full text eligible articles were then evaluated and included if they met pre-established inclusion criteria. The researchers compiled data from studies that met their eligibility criteria and organized them into disease categories. Different categories represented the diseases most often described in the studies as inflammatory diseases, neoplasms (cancers), metabolic disorders, and neurodegenerative disorders. Careful extraction of the key data from each of the selected studies was performed to allow for adequate comparison and in-depth analysis across the various data elements.

After determining the eligibility of articles based on the defined criteria of inclusion and exclusion, full-text articles were assessed. Different number of studies was selected for analysis in the qualitative and/or quantitative synthesis. This selection process was carried out following PRISMA methodology, mutual and combined screening was done to prepare this review (Figure 1).

Figure 1

PRISMA Work Flow



2.3. Data Analysis

Data analysis was done by organizing data findings across studies and to analyze the relative efficacy and limitations of each. Key findings are summarized in tables. Moreover, this review was conducted in accordance with the guidelines of systematic review research articles. All the authors participated in collecting the data and screening, while the risk of bias of the selected articles was independently assessed by two reviewers, depending on the study design. Clinical trials were assessed using the Cochrane RoB 2 instrument. Biases, such as selection, detection, and reporting biases were considered during the review process.

3. RESULTS AND DISCUSSION

3.1. Anti-inflammatory Prospective of Phytocompounds

Inflammation is a critical key response

to the pathogenic foreign invaders. It is the defensive strategy of the host against any kind of microbial/viral infection or cell injury. Inflammation can be characterized by redness, pain, heat, and swelling [8], involving the release of cytokines (interleukins i.e., 1L-6, IL-1, and Tumor Necrosis Factor (TNF-alpha), and Reactive Oxygen Species (ROS) [9]. These inflammatory disorders have been known to be treated with a number of currently available synthetic drugs, for instance NSAIDS and corticosteroids. However, the usage of these immuno-suppressive drugs is restricted due to their prolonged duration therapy linked with a number of adverse events, and their higher cost. Furthermore, oxidative stress communication is an important mediator in the mechanism of anti-inflammatory activity of phytochemicals. Oxidative stress and inflammatory mediators have close connections, whereby the oxidative state increases inflammation responses and injury. Curcumin, quercetin, resveratrol, and epigallocatechin gallate are phytochemicals with strong antioxidant properties, which eliminate ROS, upregulate endogenous antioxidants, and decrease lipid peroxidation [5]. A number of phytocompounds target multiple converging pathways involved in inflammation by modulating pro-inflammatory cytokines including NF-κB, COX-2, TNF-α, and interleukins. The ability of these compounds to target multiple pathways makes them better at suppressing inflammation compared to synthetic compounds that target one pathway alone [3]. The usage of anti-inflammatory phytocompounds (Table 1) in this regard has been considered as a safer and an effective therapeutic treatment for chronic inflammatory diseases [10].

3.2. Anti-cancer Phytocompounds

Cancer is the major public health hazard affecting 32.6 million people worldwide and resulting in deaths of more than 15 million people each year [18]. Various herbal extracts provide beneficial effects in terms of treatment and prevention of cancer in a variety of ways. These include activating DNA-repair mechanisms, by enhancing the production of certain protective enzymes (e.g., matrix metalloproteases), by enhancing immunity, by performing anti-oxidant activity, and by inhibiting the production of enzymes and hormones which are linked with the activation of cancer-causing genes [19].

Various phytocompounds, that is, epigallocatechin-3-gallate (EGCG), Cristine, vinblastine, vincristine, Alline, curcumin, genistein, and quercetin have been seen to be acting as anti-cancer agents for years. Phytosterols as specific phytocompounds resembling cholesterol in their structures are exclusively found in plants and have been seen to be acting as anti-cancer and cholesterol-lowering agents [16]. Table 2 presents a number of phytocompounds which have been seen to be acting as effective therapeutic agents in the treatment of various types of cancers. Phytocompounds perform pleiotropically by acting on cell proliferation, apoptosis, oxidative stress, and inflammatory pathways at once. This multi-target action profile enables phytocompounds to act as promising agents both as chemo-preventive and chemotherapy adjuncts [19].

Table 1. Anti-inflammatory Role of Phytocompounds and their Mechanism of Action

Phytocompounds	Source	Nature	Model	Mechanism of Action/ Targeted Pathways	Diseases	References
Resveratrol	Grapes, Red wine	Phenolic	*In vivo* Study	Reduction of B-lymphocytes and Th1 cell percentage	Systematic Lupus Erythematosus (SLE)	[11]
Apigenin	Parsley, thyme, peppermint, olives, and chamomile	Phenolic	Preclinical,, *In vivo* study	Suppression of COX-2	Systematic Lupus Erythematosus (SLE)	[12]
Astilbin	*Smilax glabra*	Phenolic	*In vitro, in vivo* study	Reduction of IL-1β, and IL-6	Systematic Lupus Erythematosus (SLE)	[13]
Curcumin	*Curcuma longa*	Phenolic	*In vivo* study	Reduction of TNF-α, NF-κB activation	Rheumatoid arthritis (RA)	[5]
Parthenolide	*Tanacetum parthenium*	Terpenoid		Downregulation of NF-κB and MAPKs	Obesity induced inflammation	[14]
Acacetin	*Robinia pseudoacacia,*	Phenolic	Preclinical study	Inhibition of iNOS and COX-2	Parkinson's disease (PD)	[9]
Epigallacto-catechin Gallate (EGCG)	*Camellia sinensis*	Phenolic	*In vivo* study	↓NLRP3 expression, IL-1β, and IL-18	Systematic Lupus erythematosus (SLE)	[15]
Naringenin	*Citrus paradise* and *Citrus sinensis*	Phenolic		Reduction of IL-1β	Diabetes induced Renal inflammation	[15]
Hesperetin	*Citrus Limon,* and *Citrus reticulata*	Phenolic	Preclinical, *In vivo* study	Reduction of TNF-α and IL-1β	Diabetes induced retinopathy	[16]
Baicalein	*Scutellaria baicalensis,*and *Oroxylum indicum*	Phenolic	*In vivo* study	Reduction of TNF-α, and IL-1β	Diabetes induced retinopathy	[17]

Table 2. Anti-cancer Activity of Phytocompounds and their Mechanism of Action

Phytocompounds	Source	Nature	Targeted Pathways	Diseases	Reference
Platycodin D	*Platycodon. grandiflorus*	Saponin	Induces apoptosis ↑caspase-3 activation and PARP cleavage	Leukemia	[20]
Oridonin	*Rabdosiae rubescens*	Terpenoid	Induces apoptosis (p=0.000) by ↓Bcl-2/Bax ratio, and increasing the expression level of PPARγ, PARP, and Fas	Breast cancer	[21]
Coptisine	*Optidis rhizome*	Alkaloid	May contribute to suppress tumor growth and reduce metastasis by the possible inhibition of the RAS-ERK pathway	Colorectal cancer	[22]
Curcumin	*Curcuma longa*	polyphenol	Upregulating P-10/AKT pathway	Breast cancer	[23]
Scutellarein	*Scutellaria barbata*	Flavonoid	Retards cancer growth and increases the concentration of mitochondrial superoxide (*in vivo* model)	Breast cancer	[24]
Isoegomaketone	*Perilla frutescens*	Phenolic compound	May suppress tumor growth (p<0.05) by affecting PI3K/Akt signaling pathway	Hepatic carcinoma	[25]

Among the various anti-cancer phytocompounds that have been studied, curcumin stands out. Curcumin hinders tumor cell growth through the inhibition of signaling pathways, such as NF-κB, PI3K/Akt, MAPK, and induction of apoptosis by means of caspases and p53. Curcumin has shown anti-proliferative properties in cases of breast and prostate cancer. Likewise, resveratrol, a polyphenol found in grapes and berries, possesses anticancer activities. This works by means of cell cycle arrest, reduction in oxidative stress, angiogenesis inhibition, and metastasis through inhibition of VEGF and MMPs [14].

Phytocompounds have numerous important limitations which restrict their potential therapeutic applications, despite their biological potential. One key limitation is their low bioavailability, as many of these compounds have low solubility, limited absorption, or rapid metabolism (therefore reducing the systemic amounts). In addition, there is a large amount of first-pass metabolism occurring in the gut and liver which may convert a significant amount of these compounds to their inactive forms, considerably reducing their pharmacologic activity. Finally, the compound's activity may also be affected by different food sources, differences in individual metabolism, and potential interactions between phytocompounds and other nutrients or medications [21].

3.3. Anti-oxidant Potential of Phytocompounds

Oxidative stress triggered by the overproduction of free radicals may result into the onset of a number of metabolic, cardiovascular, and neuro-degenerative disorders, as well as various types of cancers. The phytocompounds present in fruits, cereals, vegetables, edible algae, macro-fungi, and other medicinal plants have been seen to be exerting a strong anti-oxidant effect [26]. Thus, these are helpful in preventing the development of various chronic disorders [27]. Grapes, berries, dates, guava, plum, sweetsop, and pomegranate are rich in their phenolic contents and thus exert a high antioxidant activity. The associated targeted pathways of different phytocompounds in different diseases have been presented in Table 3. Many phytocompounds display polypharmacologic characteristics, which make them capable of influencing multiple molecular targets and signaling pathways at once. Synergistic biological effects are achieved as a result of such actions, whereby the combined activity produces better results than a single one. An illustration is provided by curcumin, which displays antioxidant, anti-inflammatory, and anti-cancer effects by means of NF-κB, and cytokines [26].

3.4. Anti-diabetic Potential of Phytocompounds

Diabetes is the secretion of insufficient insulin levels or by the insufficiency of insulin activity [19]. Various plants and plant extracts have been traditionally used as a source of anti-diabetic agents in Pakistan, India, China, and other Asian countries which are considered as a safer and a more reliable alternative to the usage of synthetic drugs available as anti-diabetic agents. A variety of anti-diabetic phytocompounds have been derived from herbal extracts of different plant species, for instance, *Anoectochilus roxbuglii*, *Bacopa monnieri*, *Bixa orellana*, *Chamaemelum nobile*, *Catharanthus roseus*, *Chicorium intybus*, *Curcuma longa*, *Costus pictus*, *Cinnamomum verum*, *Cryptolepis sanguinolenta*, and *Matricaria chamoomilla*. Phytocompounds (e.g., quercetin and resveratrol, and chicoric acid and lupinin) have been seen acting as anti-diabetic agents [33].

Table 3. Mechanisms of Action of Anti-oxidant Phytocompounds against Oxidative Stress-induced Diseases

Phytocompounds	Sources	Nature	Study/Model	Targeted Pathways	Diseases	References
Resveratrol	Red Grapes	Polyphenol	Preclinical	↑SOD, GSH	Alzheimer disease	[28]
Sulfuretin	*Albizzia julibrissin* and *Rhus verniciflua*	Flavonoid	*In vitro* study	↓ROS, ↑HO-1, ↑PI3K Akt , ↑Nrf2	Alzheimer disease	[29]
Baicalin	*Scutellaria baicalensis*	Flavone	*In vitro, in vivo* study	↓MDA, ↑GPx, SOD, HO-1, ↑pAkt	Traumatic brain injury (TBI)	[30]
Diallyl trisulfide	*Allium ramosum*	Organo-Sulphur compound	*In vitro, in vivo* study	↑Nrf2 , and HO-1 , ↑pAkt	Ischemic stroke	[31]
Brassicaphenanthrene A	*Brassica rapa*	Phenanthrene	*In vitro, in vivo* study	↑Nrf2 nuclear translocation	Alzheimer diseases	[29]
Totarol	*Podocarpus totara*	Phenolic diterpene	*In vitro, in vivo* study	↑ Nrf2 by upregulating PI3K/ Akt pathway ↑HO-1, SOD and GSH	Ischemic stroke	[32]

Table 4. Neuro-protective Potential of Phytocompounds, their Source, Nature, and Mechanism of Action

Phytocompounds	Source	Nature	Study Model	Targeted Pathways	Diseases	References
Caffeine	*Erigeron annuus*	Alkaloid	*In vitro, in vivo*	Acts as AChE-I and as an anti-oxidant, induces possible BACE inhibition	Alzheimer's disease	[37]
Theaflavin	*Camellia sinensis*	Polyphenol	*In vitro, in vivo* and preclinical study	↑Behavioral characterization ↑TH-positive cells in the ST region ↓Caspase 3, 8	Parkinson's disease	[38]
Andrographolide	*Andrographis paniculate*	Diterpenoid	*In vivo*	Activates Nrf2/Keap1-mediated HO-1 signaling pathway, ↓NF-κB, ↓PGE2 and TNF-α, iNOS and COX-2, inhibits JNK-MAPK pathway	Alzheimer's disease	[39]
Paeoniflorin	*Paeonia lactiflora*	Monoterpene glycoside	*In vitro, in vivo*	↓IL-1β, IL-6, ↓TNF-α, and NO ↑IL-10 and TGF-β1.	Alzheimer's disease	[34]
Ferulic acid	*Spinacia oleracea*	Polyphenol	*In vitro, in vivo*	↑CAT, SOD, GPx, and GSH activity by activation of Nrf2 signaling	Parkinson's disease	[19]
Ginkgolides A, B and C	*Ginkgo biloba L.*	Terpenoids	*In vitro, in vivo*	↑Akt, Nrf2, ↑Akt/CREB signaling pathway ↑pAkt, pNrf2, pCREB ↑HO-1 ↓cleaved caspase 3, Bax	Ischemic stroke	[40]

Most of the phytocompounds exert their therapeutic actions by regulating the enzymes and signaling pathways associated with glucose metabolism. For instance, berberine, derived from plants, such as *Berberis vulgaris*, enhances insulin sensitivity and reduces glucose production through activation of AMPK [13]. Curcumin displays anti-diabetic activities by inhibiting the inflammatory mediators, lowering the oxidative stress, and improving β-cell function via the regulation of NF-κB and PI3K/Akt pathways. Resveratrol, a compound found in grapes and berries, has exhibited potential to improve glucose homeostasis by activation of SIRT1 and AMPK pathways that improve insulin sensitivity and enhance mitochondrial function [21]. Quercetin and kaempferol have been reported to exert their anti-hyperglycemic effects through the inhibition of the enzymes α-glucosidase and α-amylase that delay the breakdown of carbohydrates, thus decreasing postprandial blood glucose.

Finally, EGCG found in green tea also acts on the insulin pathways to reduce oxidative stress-related cell damage [8]. Diabetic complications, such as nephropathy, neuropathy, retinopathy, and cardiovascular disorders have been found to be largely attributed to oxidative stress and chronic low-level inflammation. Phytocompounds possessing anti-oxidant and anti-inflammatory activity counter diabetic complications through ROS scavenging, improvement of endogenous anti-oxidant mechanisms, and inhibition of pro-inflammatory cytokines, such as TNF-α and IL-6. Moreover, some phytocompounds have been observed to be protective towards pancreatic β-cells, thereby maintaining proper insulin secretion [29].

3.5. Neuro-protective Phytocompounds

Neuro-degenerative disorders, being recognized as the cognitive dysfunction, are considered as the major health problem with an incidence rate of 2/1000 and account for nearly 8% deaths worldwide [34]. Table 4 describes some phytocompounds with anti-inflammatory and anti-oxidant properties improving neuronal cognition and neuronal cell survival [35]. More than 120 different types of traditional medicinal plants-based neuro-protective therapies are available in Asian countries to treat various neurological and CNS disorders. Various phytoconstituents with neuro-protective activity (e.g., phenolics, alkaloids, steroids, triterpenes, saponins, and flavonoids) are present in various plant species, such as *Bacopa monniera*, *Panax ginseng*, *Centella ariatica*, *Uncaria rhyncophylla*, *Huperzia pinoza*, *Ilex paraguariensis*, *Corydalis pinoza*, *zingiber officinalis*, and *Ziziphus pinoza* [36].

3.6. Phytocompounds as Immunomodulators

Immune system is the key protection of human body against foreign particles, pathogens, allergens, and toxins. Phytocompounds help in immunity boosting properties. They may be anti-oxidants, anti-bacterial, anti-fungal, anti-viral, and anti-tumor and may help the immune system to work safely and faster for a living body (Table 5). Engulfing pathogens, that is, phagocytosis is also an important function of body's defense mechanism.

The curcumin present in turmeric controls the immune response by directing the signaling pathways of NF-κB, JAK/STAT, and MAPK, resulting in the regulation of the production of cytokines and decreasing chronic inflammation [45].

Table 5. Immuno-modulating Phytocompounds, their Source, Nature, and Mechanism of Action

Phytocompounds	Sources	Nature/Class	Targeted Pathways	References
α-tocopherol	Nuts and seeds	Vitamin E antioxidant, anti-aging	Helpful in increasing the level of plasmatic TNF and pro-inflammatory response ($p<0.05$) (*in vitro* study)	[34]
Vitamin C	Citrus fruits	Antioxidant, anti-ageing, antioxidant, anti-inflammatory	Immunomodulatory properties (ROS) and free radical scavenging property	[39]
Berberine	*Hydrasti canadensis*	Alkaloid	Involved in the suppression of NO and TNF-α levels (*In vivo, in vitro* study)	[41]
Gallic Acid	Fruits, berries, nuts	Phenols antioxidant, and anti-inflammatory	Improves immune responses, involved in the reduction of infections	[42]
Silymarin	*Silybum marianum*	Flavonoid antioxidant, anti-allergic, and anti-inflammatory, anti-hepatic	Inhibits CD4+ cells formation, migration and proliferation, and helpful in the formation of INF-γ and IL-2 (*in vitro* and preclinical study)	[43]
Quercetin	Fruits and vegetables	Flavanol (Anticancer, chemoprotective, and anti-hepatic)	Free radical scavenger (*In vitro* study)	[42]
Mangiferin	*Mangifera indica*	Glycoside (Anticancer, anti-hepatic, antioxidant, anti-inflammatory, anti-microbial)	Maintains Th1/Th2 cytokine imbalance	[44]
Vanillic Acid	Plantago major	Phenols (Antioxidant)	IFN-γ production and involved in proliferation of lymphocyte	[45]
Kaempferol	Vegetables and herbs	Flavanol (Anti-inflammatory)	Anti-inflammatory, decreases level of ROS (*In vitro* study)	[46]
Catechin	Berries	Flavonoid (Anti-oxidant)	Maintains oxidation of LDL	[47]
Malvidin	*Prunus cerasus ledeb*	Anthocyanin (Antoxidant, anti-inflammatory, immunomodulatory, cardio-protective)	Decreases paw swelling as well as cytokines expression	[48]
3-glucoside	Blackberry	Glycoside (Anti-inflammatory)	It may support platelet function	[49]
Dopamine	Fruits and Vegetables	Cardio-modulator	Reduces oxidative stress (*in vitro* and *in vivo* study)	[50]
Withanolide	*Withania somnifera*	Steroid (Anti-inflammatory, immunomodulatory)	May suppress hypersensitivity	[51]

Likewise, resveratrol has shown potential to control T-cell activation, limit overproduction of inflammatory cytokines, and enhance the antioxidant system. EGCG in green tea has excellent anti-inflammatory and immunomodulatory effects. It works by lowering oxidative stress and preventing inflammatory mediators, such as TNF-α, IL-1β, and IL-6. Quercetin, a flavonoid obtained from fruits and vegetables, regulates the immune response through mast cell stabilization and limiting the release of histamine along with the regulation of cytokines. Some other isoflavones, including genistein obtained from soy, regulate the immune signaling pathway [43].

3.7. Phytocompounds used in Combination Therapies

Herbal combination therapies (addition of two or more phytocompounds) may serve as a better alternative to synthetic drugs in terms of their higher efficacy, reduced toxicity, and increased tolerability [52]. Phytocompounds present within these combination therapies are effective at their lower doses. For instance, the effectiveness of these combination therapies in regard to their safety, enhanced host tolerability, reduced toxicity, and the decreased number of adverse effects are linked with the usage of lower doses of phytocompounds [52]. Unlike traditional target-specific medicines, phytocompounds also have the potential to modulate several signaling pathways associated with inflammatory response, oxidative stress, angiogenesis, and immunity, thus leading to synergic therapeutic responses [24]. Quercetin is known for its antioxidant, antiviral, and anti-inflammatory activities due to the regulation of MAPK and PI3K/Akt pathways. Berberine has been shown to exert anti-diabetic and cardioprotective effects by modulating glucose metabolism, AMPK pathways, and lipid metabolism. Genistein has been observed to modulate estrogen receptors, apoptosis, and cell cycle, thus providing it with its anti-cancerous properties [19]. Table 6 presents various combinations of phytocompounds used to treat a number of different auto-immune, metabolic, cardiovascular, and neuro-degenerative disorders by acting as anti-inflammatory, anti-cancer, anti-oxidant, hepato-protective, neuro-protective, anti-diabetic, cardio-protective, and immuno-modulatory agents. However, while phytocompounds demonstrate considerable therapeutic potential, the concurrent use of these chemical entities may also produce antagonism effects that limit their overall therapeutic efficacy. There are instances wherein certain bioactive chemicals interfere with the pharmacodynamics of other chemical entities, thus minimizing the benefits derived from them [50]. Additionally, the administration of multiple phytocompounds may potentiate their toxicity, especially when relatively high doses are taken or for extended time periods. Phytocompounds have the tendency to interact with CYP450 enzymes and modify the rate and extent of drug metabolism. This phenomenon may result in herb-drug interactions, which may impact the bioavailability, clearance, and therapeutic ratio of drugs concurrently administered. Competition among phytochemicals may also take place in terms of drug metabolism since several phytoconstituents require the same metabolic pathways [21]. Many of the studies that have been published on phytocompound action are based on animal experiments or test tube studies of mechanisms, for instance, antioxidant, anti-inflammatory, and anti-cancer action. The mechanism-based preclinical phytocompounds' studies have frequently demonstrated modification of major biochemical pathways involved in regulating cellular functions, such as apoptosis, inhibition of mitosis, and control of oxidative stress [27].

Table 6. Combined Effect of Two or More Different Compounds against Different Diseases

Sr. No.	Phytocompound Combination Therapies	Pathological Condition/Disease	Model Used	Targeted Pathways	References
			Anti-inflammatory		
1	Curcumin+ Quercetin	Carrageenan-induced rheumatoid arthritis	Male Albino rats (*in vitro* and *in vivo* study)	May act as anti-oxidant agents by ↑GSH and HO-1 mRNA expression	[53]
2	Gallic Acid+ Catechin	CCl_4 mediated hepatic damage	Male Wistar rats (*In vitro* and *in vivo* study)	↓ Liver inflammation by acting as the anti-oxidant and the anti-inflammatory agents	[54]
3	Resveratrol + Curcumin	Aluminium chloride-induced neuroinflammation	Male adult Wistar rats (*in vitro* and *in vivo* study)	Decrease the expression levels of Cox-2, TNF-α, IL-1α and IL-1β	[55]
5	Silibinin + Thymol	LPS-induced inflammation	RAW 264.7 cells	Significantly prevent the expression of NO (p<0.001), ROS and COX-2 by downregulating MAPK pathways	[56]
			Anti-oxidant		
6	Caffeic Acid + 18β-Glycyrrhetinic Acid	Diabetes type-II	Adult male Albino rats (*in vitro* and *in vivo* study)	Act as strong anti-oxidant agents by increasing GSH and SOD levels and by decreasing ROs and MDA levels	[57]
7	Caffein + Caffeic Acid	LPS induced neuroinflammation and anxiety	Male Swiss Albino mice	Reduce oxidative stress by aggregating the GSH and the reduced glutathione levels (p<0.05)	[53]
8	Quercetin + α-Lipoic Acid	Aluminium chloride-induced neurotoxicity	Adult male Wistar rats (*In vitro* and *in vivo* study)	Act as the strong anti-oxidant agents by increasing the levels of reduced glutathione, GSH and SOD	[58]
9	Caffeic acid + Conjugated Lenoleic acid	Liver damage	Hep-G2 cells (*In vitro* study)	Act as anti-oxidant agents by free radical scavenging activity and enhance GSH and CAT concentration (p<0.05).	[34]

Sr. No.	Phytocompound Combination Therapies	Pathological Condition/Disease	Model Used	Targeted Pathways	References
			Anti-cancer		
10	Curcumin + Arctigenin	Prostate cancer	Androgen-sensitive LNCaP Cells	Induce cellular apoptosis by down-regulating NF-κB pathway; by targeting Akt/PI3k pathway; resulting into ↓P-IκB levels, and ↑bax/bcl-2 ratio	[11]
11	Curcumin + Resveratrol	Colon cancer	HCT-116 Cell lines (*In vitro* study)	Reduce cell proliferation and induce apoptosis (p<0.05) by down-regulating NF-κB pathway	[59]
12	Genistein + Quercetin + Biochanin	Prostate cancer	Androgen-sensitive PC-3 Cells	Induce apoptosis by down-regulating c-myc, and PCNA, ↓MApK/ERk-1/2 ↑ER-β gene expression ↑MApk/c-Jun N-terminalKinase signaling ↓gene expressions for Cyclins D1 and Cyclin E ↓bcl-2 levels ↑Caspase-3 and Bax expression	[36]
13	Curcumin+ Luteolin	Colon cancer	CL-188, and DLD-1 c3ll lines	Arrest cells' growth cycle and induce necrosis (p<0.05) by down-regulating the Notch-1, and TGNF-β Signaling Pathways	[60]
			Cardio-protective		
14	Curcumin + Luteolin	TNF-α induced inflammation in endothelial cells	EA.hy926 Cells + WEHI 78/24 Monocytes	Inhibit monocytes adhesion to the vascular endothelial cells	[40]
			Neuro-protective		
15	Caffeic Acid +	Alzheimer's Disease	Male Wistar rats (*in*	Provide neuroprotective effect by	[61]

Sr. No.	Phytocompound Combination Therapies	Pathological Condition/Disease	Model Used	Targeted Pathways	References
	Chlorogenic Acid	(AD)	*vitro* and *in vivo* study)	possible inhibition of acetyl cholin-esterase (AChE)	
16	Piperine + Curcumin	Olfactory bul-bectomy-induced depression	Male Wistar rats (*In vitro* and *in vivo* study)	Suppress neuro-inflammatory and apoptotic signaling cascades by Lowering brain TNF-α levels, and the Caspase-3 levels	[62]
17	Ginkgolide B + Proto-catechuic acid	Parkinson's Disease (PD)	PC12 Cells treated with Retonone (*In vitro* study)	Decrease the expression level of mi-tochondrial apoptotic proteins, that is, Bax, Caspase-3 and cytochrome C. May inhibit apoptosis by increasing the expression level of Bcl-2	[63]
18	Curcumin + Resveratrol	Aluminium chlo-ride-induced neuro-inflammation	Male adult Wistar rats (*In vitro* and *in vivo* study)	Significantly increase the expression level of neuro-protective apuri-nic/apyrimidinic endonuclease (APE1) and maintain high levels of let-7c miRNA expression; along with decreasing the expression lev-els of Cox-2, TNF-α, IL-1α and IL-1β	[55]
19	Quercetin + α-lipoic acid	Aluminium chlo-ride-induced neuro-toxicity	Adult male Wistar rats (*In vitro* and *in vivo* study)	Act as the Acetyl-cholinesterase in-hibitors; and the strong anti-oxidant agents, that is, ↑GSH and SOD	[59]
			Anti-diabetic		
20	Caffeic Acid + 18β-Glycyrrhetinic Acid	Diabetes type-II	Adult male Albino rats (*in vitro* and *in vivo* study)	↑Insulin levels and ↓ plasma glucose levels; by associated inhibition of glucose-6-phosphatase (G6P-ase), and increasing the activity of gluco-kinase (GK) in liver	[57]
21	Baicalein + Acarbose	Hyperglycemic	SD rats (*In vitro* and	Prevent hyperglycemia by	[64]

Sr. No.	Phytocompound Combination Therapies	Pathological Condition/Disease	Model Used	Targeted Pathways	References
		conditions	*in vivo* study)	synergistic non-competitive inhibition of α-glycosidase, in gut	
			Hepato-protective		
22	Berberine + Curcumin	Non-alcoholic fatty liver	Male Sprague Dawley (S.D) Rats	Decrease the countenance of sterol-regulatory element-binding transcription factor1(SETF-1)	[65]
23	Gallic Acid + Catechin	CCl-4 mediated hepatic damage	Male Wistar Rats (*In vitro* and *in vivo* study)	↓ Liver inflammation by acting as the anti-oxidant; by increasing the level CAT and GSH,	[54]
24	Caffeic Acid + Conjugated Linoleic Acid	Liver damage	Hep-G2 Cells (*In vitro* study)	Act as anti-oxidant agents by free radical scavenging activity, ↓ mitochondrial lactate dehydrogenase (DH) leakage	[34]
			Immuno-modulator		
25	Apigenin + Luteolin	Microglia-associated neuro-inflammation	Murine cultured microglial cells, N9-microglial cells	Modulate IFN-γ induced CD-40 expression within microglial cells b targeting STAT-1 signaling pathway; hindering STAT-1 activation by inhibiting the phosphorylation of STAT-1 serine-727 residue	[66]

Still, there is only limited evidence available to support their safety and efficacy in human subjects. Although the volume of clinical data is increasing, the current volume of clinical studies is limited and extremely variable with a small number of patients in each study, short duration of intervention, and variability of study designs. Therefore, phytocompounds show practical potential but currently have an overall level of evidence that is moderate to low. More comprehensive and highly controlled clinical trials are needed to determine the safety and effectiveness in human beings [54].

These findings are consistent with a previous *in vivo* study (as well as with prior clinical studies). The study showed that exposure to phytocompounds improved several biomarkers of diseases and had the potential to reconfigure the way diseases are treated. The improvements seen here can be expected to have occurred using phytocompounds across multiple experimental models [41]. While generally the same improvements are expected (although the degree of the improvement varies by study), they may occur differently among numerous populations studied as a result of various factors. These include dosage and formulation of the phytocompounds used, length of exposure, and potentially, the individual characteristics of each subject. Additionally, potential explanations for the observed differences between experimental and clinical data include differences in bioavailability and metabolism [62].

3.8. Strength of Evidence and Limitations

The active metabolites rather than the parent compounds are not sufficiently assessed since standard cell lines lack metabolic processes. The inconsistency of assay techniques, growth conditions, and cell type selections may affect generalization (generalizability), as well as reproducibility of results. Animal models do provide better insights into the biological mechanisms underlying *in vivo* studies but have limitations. First off, there is always the possibility that animals would respond to a compound differently than human beings due to differences between the two species in their ways of metabolizing that compound and their metabolic pathways (how they breakdown and absorb). Moreover, another example would be if a study was completed using the intraperitoneal method of administration (administration of a drug directly into the abdomen) vs. oral method of administration. Since most medications are absorbed through the digestive tract and into the blood before being distributed throughout the body, if a study is conducted using the IP method of delivery, it may not provide reliable information due to a difference in dosing schedule. In addition to differences in metabolic pathways, many human populations have large amounts of genetics, dietary, and environmental variability. Therefore, laboratory experiments do not fully represent human populations. A big problem in the field is the absence of standardization since the amount and the composition of the active compounds may differ according to the plant species, geographic location, harvest circumstances, and the method of extraction used. Moreover, pharmacokinetics can be problematic owing to the low solubility, poor bioavailability, rapid metabolism, and unpredictable absorption. Moreover, another issue that should be mentioned here concerns the variability in doses as it is sometimes difficult to know the effective dose of the substance. Reproducibility is another issue due to different methods applied when preparing formulations and conducting experiments. Large clinical studies and pharmacokinetic-pharmacodynamic researches are needed to

ensure reproducibility and promote the transition of plant-derived compounds into clinically proven therapy. Finally, there are limitations to conduct long-term studies due to ethical reasons or the length of time it takes to perform between an initial trial and the final follow-up.

3.9. Conclusion

Phytocompounds have gained considerable importance in the pharmaceutical industry due to their efficacy, safety, unique properties, and modes of action. These phytocompounds have gained attention as alternatives to various conventional medicines which comparatively have more side effects and less benefits. This review aimed to summarize the current evidences on the therapeutic mechanisms of phytocompounds and their potential in drug development. Some phytocompounds are very specific and act on associated targets but some may be destroyed due to first-pass metabolism. Due to this problem, the neuro-protective and renal-protective phytocompounds are smaller in number Combination therapies for different phytocompounds might be proved as the best and distinctive solution to this problem as one phytocompound may mask the side effect (s) of another and combination of different phytocompounds can increase the health benefits. This review is hoped to support future research initiatives to either develop new medicinal plant-based medications for the treatment of diseases or carry out clinical studies to show the benefits of phytochemistry of medicinal plants.

Author Contribution

Sumaira Sharif: Writing original draft. **Quindeel Naveed:** Writing original draft, editing. **Anzeela Ghaffar:** Writing original draft, conceptualization. **Ghulam Mustafa:** Data curation, formal analysis, **Asia Atta:** Editing, resources. **Iffat Nayila:** Writing original draft. **Hafsa Malik:** Data curation, formal analysis.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

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