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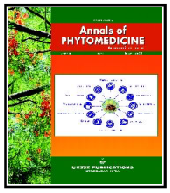

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Herbs that heal: Nature's pharmacy endowed remedies for better health

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Abstract

Today, humans have incorporated the indiscriminate use of chemicals in their daily routine. This includes the inhalation of undesired pollutants, consumption of food adulterants, synthetic insecticides and pesticides used for increasing yield and the medicines consumed for health/therapy. The allopathic medicines contain besides the active pharmaceutical ingredient, many more excipients like binders, fillers, disintegrators, flavors, colors, and preservatives. All these are known to cause adverse side effects, and thus the healer components themselves are fast transforming into causative agents for disorders.

It is believed that even today a large population treats itself using traditional medicines, wherein plants, herbs and spices are used. The same has also been acknowledged by the WHO, which launched the traditional medicine strategy (2014-2023), with the aim to keep the world population healthy by prioritizing the use of traditional and complementary medicines. Many herbs and spices are now researched by scientists to give a logical understanding of their use for prevention and treatment of common illnesses. The world today is now accepting traditional medicines not only for cure but also for wellbeing. Plant-based herbal remedies are considered to be safe as they are obtained from natural resources.

The current article bears the objective to highlight the utility of three common spices, which are an integral ingredient of cuisines across the globe. The herbal warriors considered are: *Syzygium aromaticum* (L.) Merril and Perry (clove), *Piper nigrum* L. (black pepper) and *Cuminum cyminum* L. (cumin). The article brings to light the scientific foundation to the utility of these spices as therapeutic agent for multiple diseases as well as to maintain holistic wellbeing.

1. Introduction

Human race has been dependent on mother nature for maintaining good health. Thus, not only are plants used as food but also to enhance the taste of food with their utility as medicines being on rise. History is testimony to the use of herbs for medicinal purposes in ancient India, China, Rome, Thailand amongst many old civilizations. Plants hold potential in treatment of not only communicable diseases but also the non-communicable ones (Salehi *et al.*, 2020).

Prehistoric Sumeria, has depictions of hundreds of medicinal plants enlisted on clay tablets. Similarly, Egyptian Ebers Papyrus has over 800 plants mentioned for its medicinal properties. Indian science of ayurveda, unnani, siddhi documents, support the usage of medicinal plants for therapy as well as to maintain health. Sushruta Samhita, Rig and Atharva Veda mention use of spices and herbs for healthy being (Godswill, 2019). Nineteeth century witnessed a radical shift in the role of medicinal plants due to the advancements in the field of chemical analyses. Amongst the first isolated and purified phytochemical for medicinal use was morphine from poppy in 1826 (Atanasov *et al.*, 2015). The thrust in pharmaceutical research was triggered by the two world wars, wherein not only plants but natural resources as microorganisms were screened for antibiotics, largely inspired by Alexander Flemings discovery of penicillin. Thereafter, major classes of drugs like antidiabetic, antifungal, antiparasitics, antimalarials, antihyperlipedemia, immunosuppressants, anticancer drugs, *etc*., are all synthesized from natural sources, especially plants (Harvey, 2008).

Rough estimates suggest that close to 70% population especially in the developing countries relies on traditional medicine, using herbs for primary healthcare (Jeelani *et al.*, 2018). On the other hand, developed nations too are dependent on medicinal plants though indirectly, as the raw material for commercial pharmaceutical products is largely sourced from plants (Munasinghe, 2010). Further, as per Foodtank Health of Medicinal Plants, 25% list in pharmacopeia as well as 27 of 150 top prescription drugs, are plant-based.

Amongst the plants, herbs and spices find a special importance for they hold rich potential as medicines. The volume of spice production has increased from 500 to 1800 metric tons between 2000 and 2018, while the global market is projected to grow at a CAGR of 4.7%, during 2020-2025 (Mordor Intelligence, 2020).The major contributor to this surge is the utilization of a wide range of spices for health benefits as well as therapeutic effects.

The medicinal properties of spices are attributed to a wide range of phytochemicals which are the biologically active compounds. These

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chemicals, termed bioactive, provide aroma, color, property of preservatives, as well as the properties for use as medicines. As per the National Institute of Health (NIH), bioactive food components are defined as "constituents in foods or dietary supplements, other than those needed to meet basic human nutritional needs, which are responsible for changes in health status." They thus are not nutrients but facilitate perform essential functions in the body like, (a) influence physiological function; (b) alter risk for a disease; (c) work as enzyme inducers/inhibitors of enzymes/gene (Embuscado, 2019).

In the last three decades, conscious efforts by scientists have substantiated the ancient literature of spices for health improvement, with scientific documentation (Sharifi-Rad *et al.*, 2018). Amongst the bioactives, the secondary metabolites or the phytochemicals have been established by years of research to have potential biological activity (Ahn, 2017). The array of phytoconstituents in plants, *viz.*, tannins, alkaloids, flavonoids, saponins, steroids, terpenoids, glycosides, *etc*., have been rationalized to be pharmacologically active against disorders/diseases (Parasurman *et al.*, 2014).

The current article presents the multiple pharmacological uses of three common spices that find immense use in most culinary preparations. The spices discussed are *Syzygium aromaticum* or clove, *Piper nigrum* L., referred as black pepper and *Cuminum cyminum* L. commonly called cumin. These spices are commonly used in household across the globe for enriching flavors and satiety of food. They nevertheless have hordes of phytoconstituents which can prove beneficial for maintaining holistic wellbeing as well as for treatment in case of disease/disorders.

2. *Syzygium aromaticum* (L.) Merril and Perry (Clove)

S. aromaticum commonly known as clove (Mirtaceae family), is the dried flower bud of a median size tree and believed to be a native of Maluku islands in east Indonesia. The major producers of this spice are West Indies, Madagascar and Tanzania, along with India, Malaysia and Sri Lanka. The collection of flower buds is in the maturation phase before flowering.

Cloves have been used since 2000 years by humans for its medicinal properties (Rahim, 2006). Traditionally, the oil has been used for treatment of burns, cuts, dental care, especially to alleviate toothache, as an antimicrobial, antifungal, anticarcinogenic, antiallergic and antimutagenic (Kamatou *et al.*, 2014; Chaieb *et al.*, 2007).

2.1 Chemical composition

The source of essential oils from *S. aromaticum* could be from the bud oil or leaf and the individual composition of the oil from each source varies. However, the main components have been found to be eugenol, eugenol acetate and β-caryophyllene as per GC-MS analysis (Chaieb *et al.*, 2007; Lee and Shibamoto, 2002), and is depicted in Table 1. The oil from the stem of *S. aromaticum* is not used for commercially purposes as it holds less aroma, though Patil and Dhale (2013), reported higher content of free eugenol in the same. The nutritional composition of clove is depicted in Table 2 (Ereifej *et al.*,2015).

Table 1: Composition of essential oils in clove (GS-MS analysis)

Component	Percentage
Eugenol	88.58535
Eugenyl acetate	5.62086
β-caryophyllene	1.38830
2-heptanone	0.93232
Ethyl hexanoate	0.66098
(E)-β-ocimene	0.33
Humulenol	0.27527
α-humulene	0.19985
p-allyl phenol	0.19
Calacorene	0.11437
A-copaene	0.10
Calamenene	0.10538

Table 2: Nutritional composition of black pepper per 100 g.

Constituents	Composition
Food energy	323 (kcal)
Water	5.40-6.86 (g)
Carbohydrates	31 (g)
Protein	9.3 (g)
Fat	4.3 (g)
Calcium	117.5 (mg)
Magnesium	196.8 (mg)
Phosphorus	1.6 (mg)
Sodium	61.6 (mg)
Potassium	111.6 (mg)
Iron	8.3 (mg)
Zinc	1.4 (mg)
Thiamine	0.1 (mg)
Copper	0.4 (mg)

The rich array of phytoconstituents in clove, has made clove a spice not only used in food but also as a nutraceutical. The important derivatives of eugenol, the prominent phytoconstituent are depicted in Figure 1 (Pisano *et al.*, 2007). Some of the pharmacological uses of cloves are mentioned herewith.

2.2 Antioxidant

The human body during the normal metabolic and physiological functions generates reactive oxygen species (ROS) which are potent destructors of crucial biomolecules as nucleic acids, lipids, proteins as well as carbohydrates. They have ability to cause DNA damage which may lead to mutation (Çakýr *et al.*, 2006). Absence of ROS scavenging mechanism leads to disease conditions (Gülçin *et al.*, 2004).

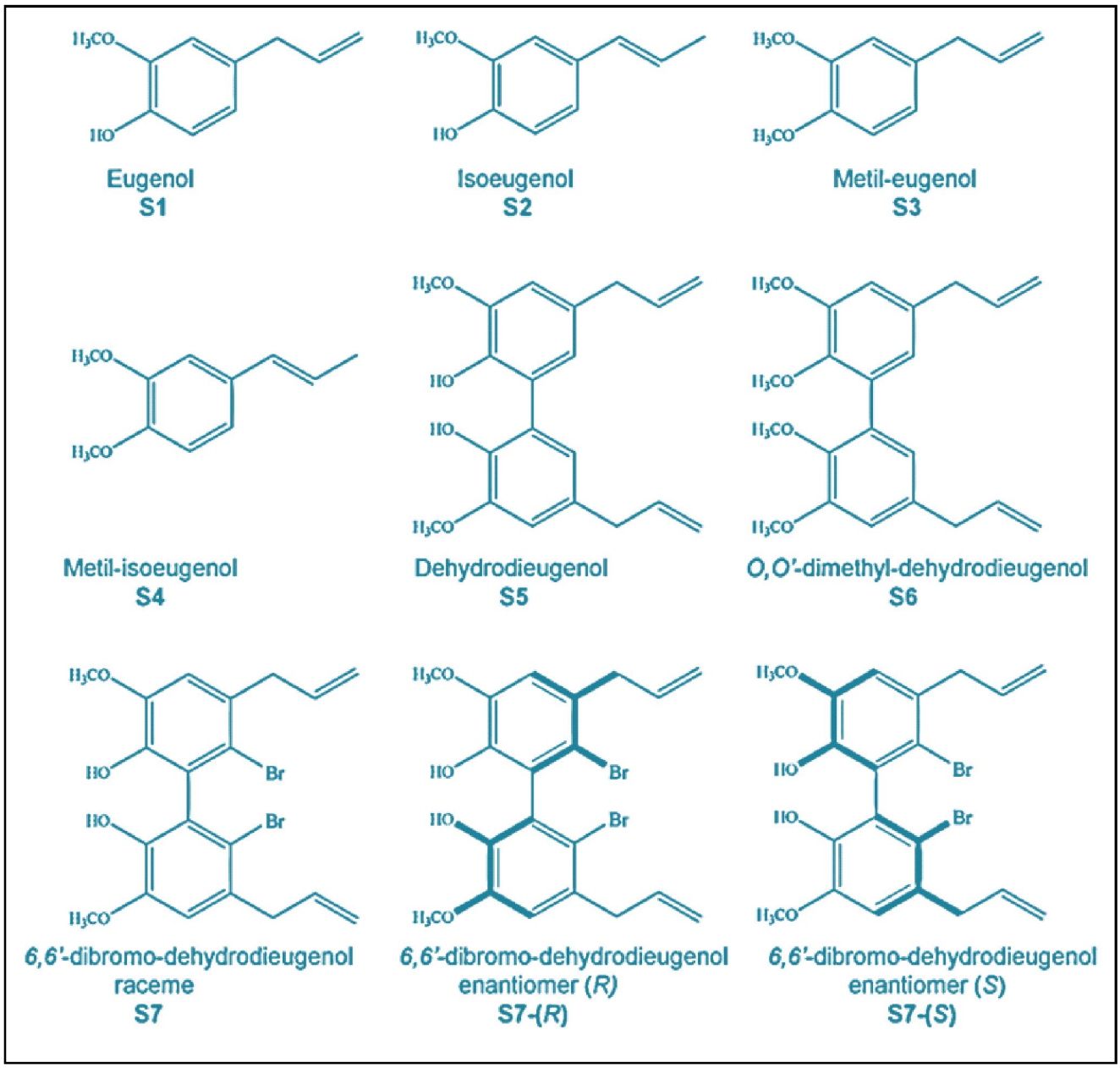

Figure 1: Eugenol and its derivatives in aromatic oil of clove.

Clove has been identified as a potent antioxidant due to the good concentration of phenolics as eugenol and eugenol acetate. A comparative *in vitro* antioxidant activity study of clove with synthetic food preservative, butylated hydroxytoluene (BHT), was conducted by Bamdad *et al.* (2006). The antioxidant activity using 1,1-diphenyl-2-picryl hydroxyl (DPPH) radical, ferric thiocyanate, hydroxyl radical and reducing power model systems was determined. The study concluded that the antioxidant activities of clove was comparable with BHT. A similar observation was reported by Gülçin *et al.* (2004), wherein multiple synthetic antioxidants were used, and the DPPH radical scavenging activity was reported to be maximum for clove oil (trolox< butylated hydroxyanisole < alfatocopherol < BHT < clove oil). Gülcin *et al.* (2013) established the structure-activity relationship by *in vitro* methods in comparison to BHT, trolox and α-tocopherol where in eugenol produced highest antioxidant activity. The eugenol molecule has an interesting conjugation of aromatic ring with the carbon chain stabilizing the phenoxyl radical by resonance. Eugenol thus reduces 2 or more DPPH radicals, inspite of only one hydrogen (from hydroxyl group) and, is thus multifunctional and mediates as a singlet oxygen scavenger, reducing agent as well as hydrogen atom donor.

A comparison of eugenol (50 µm) with alpha-tocopherol and ascorbic acid revealed increase to the tune of 2.35, 5.1 and 3.6 times in superoxide scavenging ability, iron reducing ability, reducing power, respectively. With such significant antioxidant properties, it can be effective for maintaining good health (Parween *et al.*, 2020).

The antioxidant potential of aqueous and alcohol extracts of a clove along with other spices, suggested that phenolic compounds and the flavonoids provide antioxidant potential. Lipid peroxidation was inhibited in a dose dependent manner by many spices wherein the activity was maximum for clove (Khan *et al.*, 2012). Similar observations have been reported by Ghadermazi *et al.* (2017), wherein clove oil was most potent antioxidant followed by oils obtained from oregano and sage.

Pérez-Rosés *et al.* (2016), revealed that stimulated ROS and nitric oxide production in human neutrophils is inhibited by clove oil while high myeloperoxidase (MPO) inhibition was observed in human leukocytes.

Memory defects can result due to oxidative stress, and hence antioxidants hold potential as a therapeutic agent for treatment is such cases. Pretreatment with clove oil decreased the oxidative stress and was able to revert learning deficits as well as memory (Mehta *et al.*, (2018).

2.3 Anti-inflammatory and analgesic

Inflammation is an innate immune response to variety of invaders exerting protection but at the same time, it has the potential to become harmful in the chronic manner, like the cytokine storm in case of COVID-19.

The use of clove oil as an anti-inflammatory and analgesic for tooth ache has been known since centuries. Hwang *et al.* (2020), suggested that inhibition of voltage-gated sodium channels present in the teeth neurons provide, anti-inflammatory and analgesic properties.

In the neutrophils, inhibition of superoxide anion production is mediated *via* the pathway involving Raf/MEK/ERK1/2/p47-phosphorylation. Due to this, the production of pro-inflammatory mediators, namely; IL-6, IL-1, TNF-alpha, prostaglandin E2 and nuclear factor expression, are inhibited. Thus, the anti-inflammatory activity of the major constituent of clove oil eugenol relates to the prevention of chemotaxis of neutrophils and macrophages along with the inhibition of the synthesis of prostaglandins and leukotrienes as well as cytokine receptor expression on macrophages (Baitha *et al.* 2020; De Andrade *et al.* 2020; Pytko-Polo *et al.* 2016).

In silico studies suggest that eugenol may inhibit not only COX-2 but also 5-LOX. Thus, eugenol from clove can prove to be a replacement of nonsteroidal anti-inflammatory drugs used for multiple diseases like inflammatory osteoarthritis (De Andrade and Mendes, 2016).

The analgesic activity has been attributed to the activation of calcium and chloride channels in the ganglionar cells, voltage dependent sodium and calcium channels in the trigeminal ganglion and the action as capsaicin agonist (Daniel *et al.*, 2009).

Barboza (2018) reviewed the anti-inflammatory nature of eugenol and concluded that expression of various inflammatory mediators, as IL-6, IL-1, IL-4, IL-5, TNF-α, NF-κB, iNOS, NO and COX-2, was diminished, whereas that of antioxidant enzymes as glutathione peroxidase, catalase, superoxide dismutase, and glutathione peroxidase showed an upward trend. It was observed that eugenol has effects on the arachidonic acid derived inflammatory mediators of inflammation wherein the synthesis of prostaglandins and leukotrienes decreases leading to decline in edema. In human platelets, eugenol, the active ingredient in clove oil stimulated aggregation. Compounds structurally similar like methyl-eugenol in cerebral ischemic models lead to an increase in activity of catalase and superoxide dismutase, along with inhibition of NO production. The production of pro-inflammatory cytokines showed a decrease with an increase in the anti-inflammatory cytokines, proving its utility for ischemia-related inflammatory diseases (de Cássia da Silveira *et al.*, 2014). The leukocyte rolling, adhesion, and migration has also been reported to lessen in presence of eugenol (Estevao-Silva *et al.*, 2014). Suppression of Th2 immune response in animal models with ovalbumin induced allergic asthma, was observed as the eosinophil lung tissue infiltration was reduced and so were the levels of IgE, IL-4 and IL-5 (Magalhaes *et al.*, 2019). As stated earlier, evidence are enough to suggest eugenol as an effective antioxidant, thereby inhibiting NF-B activation, cyclooxygenase-2, prostaglandin synthesis, and reducing level of inflammatory cytokines (Fathy *et al.*,2019).

2.4 Antibacterial, antiviral and antifungal

Clove has been used to cure infections not only bacterial in origin but also as an antiviral and antifungal. This property has been ascribed to the presence of free OH group in eugenol structure. Further, it is a hydrophobic molecule and so it can penetrate the lipopolysac charide cell membrane, especially in gram-negative bacteria, like *S. aureus, P. aeruginosa*, and *E. coli*gaining entry into the cell. The damage to the cytoplasmic membrane, thus leads to the intracellular components, being leaked, leading to cell death (Magdalena and Olas, 2021). Further, eugenol's hydroxyl group binds to active site on histidine carboxylase, protease, and amylase in *E.aerogenes* (Marchese *et al.*, 2017), inhibiting the enzyme action while in *E.coli* and *L. monocytogenes*, inhibition of membrane-bound ATPase in observed (Gill *et al.* 2006). Hyldgaard *et al.* (2012), proposed that in presence of eugenol intracellular ROS are produced, leading to damaging of DNA, disruption of cell membrane and cell death.

For *S. agalactiae* isolates, which can cause several infections like urinary tract infection and meningitis, growth inhibition was observed even in erythromycin and clindamycin resistant variants, as protein and lipid leakage from the cytoplasm due to cell membrane disruption was observed (Biasi-Garbin *et al.*, 2015). Carbapenem-resistant, *K. pneumoniae*, is substantial hazard, and can lead to fatal infections. Qian *et al.* (2019), demonstrated eugenol to possess concentration dependent antimicrobial activity against this strain. It leads to the cell membrane becoming hyperpolarized with an increase in permeability, leading to cell rupture.

Biofilms on implants used in medicine are a persistent source of infection. Clove oil is an inhibitor towards development of such biofilms as it not only prevents its formation by dispersing the cells but also reduces the viability of cells leading to inactivation. The eugenol hinders elastase, violacein, and pyocyanin production thereby preventing the formation of biofilms involving *S. enteritidis*, one of the multi-resistant strains (Mak *et al.*, 2019).

Antiviral activity against both HSV-1 and HSV-2, has been observed with clove oil, and in combination with acyclovir, an antiviral agent, the effect was synergistic. The antiviral effect is due to the inhibition of viral replication which limits the spread of infection (Mak *et al.*, 2019). In the current COVID-19 pandemic, cloves along with cinnamon, ginger, black pepper, garlic, neem, and basil are prospective candidates for therapy (Mehrotra, 2020; Singh *et al.*, 2021).

Computational studies have reported many phytoconstituents of clove as effective candidates for drug development against COVID-19 (Pandey *et al.*, 2020; Joshi 2020). The most potent one is kaempferol, which can bind with high affinity to the SARS-CoV-2 substrate binding pocket of the main protease. *In silico* studies reveal that this hydrophobic interaction with flavonoids, is suggestive of SARS-CoV-2 inhibitory activity. Compounds as bicornin and biflorin depict high affinity for Mpro, and also possess potential inhibitory activity against the virus through molecular docking studies (Rehman *et al.*, 2020).

Besides being antimicrobial and antiviral, eugenol is also an effective antifungal as the virulence factors are inhibited, cell membrane integrity is lost, affecting the function along with inhibition of biofilm formation. It shows inhibitory activity against a large number of fungi, as *C. albicans*, *S. cerevisiae*, *P. glabrum*, *P. italicum*, *A. niger*, *F. oxysporum*, *etc.* (Batiha 2020; Mak *et al.*, 2019; Marchese *et al.*, 2017).

2.5 Anticarcinogenic

Therapy for malignancy needs to target the inhibition of anomalous cell growth and preferably killing of all such cells. Extracts of *S. aromaticum* contain multiple phytochemicals, namely; tannins and eugenol. *In vitro* studies on human promyelocytic leukemia cells, suggests that eugenol from clove induces apoptosis, thereby inhibiting mutation (Yoo *et al.*, 2005) Batiha *et al.* (2020) confirmed that the anticarcinogenic activity of clove extracts could be attributed to presence of tannins.

Fangjun and Zahijia (2018) suggest that eugenol may have chemotherapeutic properties against human lung cancer. On two cell lines, *viz.*, human embryonic lung fibroblast and lung adenocarcinoma, eugenol was found to impede infiltration of carcinogen, thereby reducing cell viability and preventing the metastasis. The molecular mechanisms involved in cell cycle regulation, namely; PI3K/Akt pathway and matrix metalloproteinase pathway are inhibited.

Cisplatin is a known anti-carcinogenic drug and combination with eugenol leads to higher cytotoxic effects in breast tumors (Islam *et al.*, 2018). The combination improves the inhibition of aldehyde dehydrogenases and enhances the inhibition of NF-κB signaling pathway. Similar effects wherein the sensitivity of cervical cancer (HeLa) is increased was observed when cisplantin and eugenol were used together.

Using an animal model, eugenol from cloves not only affects the progression of the tumor, but it reduced its size. Further, inflammatory markers as IL-6, cyclooxygenase-2, tumor necrosis factor-alpha, nitric oxide synthase and prostaglandin are reduced (Ghosh *et al.*, 2005). It has been suggested that rate of apoptosis is stimulated, c-Myc and H-ras oncogene expression is down regulated. The rate of cell proliferation is inhibited, there by restricting skin carcinogenesis (Pal *et al.*, 2010).

2.6 Other pharmacological uses

Cloves have been bought to many more medicinal uses since centuries. Its use as an antidiabetic agent is well known. The ethanoic clove extract possesses human peroxisome proliferator, activated receptor-γ ligand-binding activity in a GAL4-PPAR-γ chimera assay, which significantly suppressed the blood glucose increase in type 2 diabetic mice (Kuroda *et al.*, 2012). *In vitro* studies by Mehrotra *et al.* (2020) suggest that a dose-dependently inhibition is observed by acetone extracts of clove towards α-glucosidase with an IC50 value of 148.27 µg/ml.

Clove oil is effective as an insecticide against *Pediculus capitis*, the common human headlouse (Yang *et al.*, 2003). Clove oil has been used as a mosquito repellent, being effective against anopheles, aedes and culex mosquitoes (Trongtokit *et al.*, 2005).

Aqueous extract of *S. aromaticum* depicts low efficacy potential as anticonvulsant due to presence of alkaloids, flavonoids, and tannins and has potential for seizure management (Ali, 2019).

Clove phytochemicals, namely; gallic acid, ellagic acid, tannins, flavonoids and glycosides, known to possess use as an antithrombotic, antiprotozoal, gastroprotective, and aphrodisiac efficacy. Traditionally, it has been extensively used for mitigating indigestion complaints like flatulence, and even diarrhea (Idowu *et al.*, 2021).

Main constituent of clove oil, eugenol can prevent blood clots as it shows activity as a platelet inhibitor. It has been shown to be exhibit inhibitory activity against arachidonic acid-induced platelet aggregation, as well as synthesis of prostagland in thromboxane B2. A comparison of the golden standard acetyl salicylic acid suggests that combination of acetyl eugenol along with eugenol is more effective in inhibiting platelet aggregation (García-Mediavilla, 2007).

3. *Piper nigrum* L. (Black pepper)

P. nigrum, commonly called black pepper, is a member of family Piperaceae. It is a perennial shrub cultivated in tropical regions. The plant fruit is dried, and the peppercorns, thus formed are majorly used in every house for seasoning. Its taste and aroma is very pungent, and pepper is often referred to as 'King of spices'. As per 2020, Ethiopia is largest producer as well as exporter of pepper in the world. Vietnam, Indonesia, Brazil, India, Malaysia, and China are other major producers of the spice.

Table 3: Nutritional composition of black pepper per 100 g

Constituents	Composition
Food energy	400.0 (kcal)
Water	8.0 (g)
Carbohydrates	66.5 (g)
Protein	10.0 (g)
Fat	10.2 (g)
Calcium	0.4 (g)
Phosphorus	160.0 (mg)
Sodium	10.0 (mg)
Potassium	1200.0 (mg)
Iron	17.0 (mg)
Thiamine	0.07 (mg)
Riboflavin	0.210 (mg)
Niacin	0.8 (mg)
Ash	4.6 (g)

The constituents in pepper can be categorized as the pungent compounds and the volatile oil. The pungency of black pepper can be ascribed mainly to piperine, chemically named trans, trans-5-(3,4-methylenedi-oxyphenyl)- 2, 4-pentadienoic acid piperidide. (Traxler, 1971). The black pepper hull is rich in essential oils and fiber. The general composition is volatile oil 2.0–2.6% wherein the major constituents are depicted in Table 3 (Narayanan, 2000) and oleoresin 6-13%. The nutritional composition is depicted in Table 4 (Tainter and Grenis, 1993).

Table 4: Average composition of volatile compounds in black pepper

Compound	Composition (%)
β-caryophyllene	23.59
Limonene	21.06
β-pinene	11.08
Sabinene	8.50
α-pinene	5.28
α -cubebene/δ-elemene	3.25
α-3-carene	2.82
Myrcene	2.23
α - amorphene	1.51
α - thujene	0.73
α - phellendrene	0.68
α - terpinylacetate	0.86
α - copaene	0.82
ar - curcumene	0.26

Amongst the phytoconstituents are mainly phenols, alkaloids, and flavonoids. The major constituents in its essential oil are α-pinene, β-pinene, dl-limonene, linalool, α-phellandrene, piperonal, caryophyllene, cryptone, citronellol, citral, sabinene and many more. Figure 2 depicts the structures of the most prominent constituents (Zachariah and Parthasarthy, 2012).

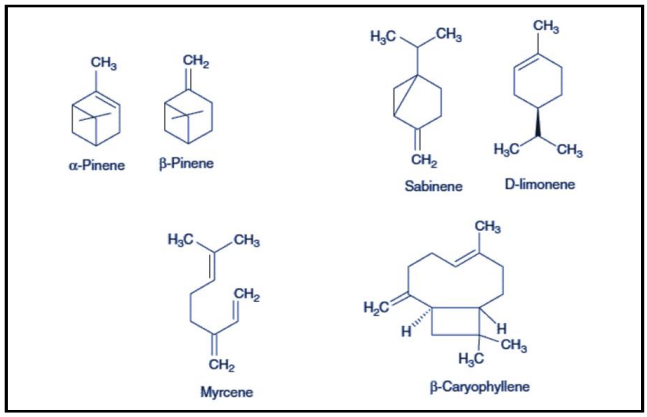

Figure 2 : Structure of prominent constituents of black pepper.

3.1 Antioxidant

Oxidative stress results due to tissue damage during metabolic processes. To counteract this damage, the level of tissue antioxidants needs to be enriched. Piperine in pepper is an effective antioxidant and protects the tissue damage caused due to free radicals. It has been suggested that pepper helps reduce oxidative stress, resulting from a diet rich in fat by maintaining the enzymatic antioxidants levels. The parameters considered were superoxide dismutase, catalase, glutathione peroxidase, glutathione-s-transferase and also cellular glutathione (Vijay Kumar *et al.*, 2004). Damanhouri and Ahmad (2014) suggested that as pepper holds free radical scavenging activity, it delays ageing, and this radical scavenging activity could be ascribed to the presence of phenols and flavonoid. Comparative studies of pepper oil with standard antioxidants as butylated hydroxy toluene and butylated hydroxy anisole suggest their antioxidant potential are at par (Kapoor *et al.*, 2005 and 2013; Singh *et al.*, 2005). Sapam *et al.* (2018), have compiled together the antioxidant potential of extracts of phytoconstituents of *P. nigrum* using different solvents and found good activity. At an oral dose of 50 and 100 mg/kg, given for 21 days, to Alzheimer disease rat models, a methanolic extract enhances memory as well as antioxidant potency. Other species of pepper as *P. guineense* and *P. umbellatum* also have shown to protect the functioning of heart liver and kidney in hamster's fed with atherogenic diet for 12 weeks. The diet lead to increased oxidative stress, with alterations in lipid profile and antioxidant enzyme activities, which was significantly bought to normal levels after the piper extract administration (Agbor *et al.*, 2012).

3.2 Immunomodulatory

Black pepper exhibits immunomodulatory effects and helps boost immune cell function as not only is the functioning of immune cells improved, but it also helps in proliferation of the cells. Thus, pepper is effective in putting forward a powerful resistance to infections caused by various microorganisms (Majdalawieh and Carr, 2010). The propagation of splenocyte increases in presence of an aqueous extract of black pepper in a dose dependent manner along with a fall in Th_1 cytokine secretions. The role of nitric oxide in the immune system is immense and pepper has been found to amplify its production and secretion of the same by macrophages (Bernardo, 2010). Pepper is a potent immunomodulator as IL-4 and 10, the Th_2 cytokines secretion is suppressed while cytokines of Th_1 family as IFNγ is improved. The effect is also seen on NK cells wherein the cytotoxic activity is enriched (Majdalawieh and Carr, 2010). Extract of pepper interfers with the immunological role of macrophages, inhibiting the secretion of anti-inflammatory cytokines and also the LPS-induced death (Ngoci *et al.*, 2011). Piperine from pepper has during *in vitro* studies led to the conclusion that the immune response sensitization is activated by lipopolysaccharides while IgM concentration is reduced along with reduction in the expression of cluster of differentiations (Lee *et al.*, 2018). Piperine from pepper has during *in vitro* studies led to the conclusion that the immune response sensitization is activated by lipopolysaccharides while IgM concentration is reduced along with reduction the expression of cluster of differentiations (Lee *et al.*, 2018).

3.3 Anticarcinogenic

The potential of *P. nigrum* as an antitumor has been studied in animal models as well as *in vitro*. The major constituent in pepper,

piperine, has been hypothesized to be the most important component leading to cancer-battling properties (Zheng *et al.*, 2017; Makhov *et al.*, 2012). Piperine has been effective against lipid peroxidation along with activation of enzymatic antioxidants, and thus helps reduce lung cancer. The associated unsaturated amides along with its potential as an antioxidant help in prevention of carcinogenesis (Doucette *et al.*, 2013).

Angiogenesis is the key for tumor growth and the same can be inhibited by phosphorylation of Thr 308 and Ser 473 of protein kinase B. Thus, the G1/S transition is inhibited, and the proliferation terminated, in presence of piperine (Yaffee *et al.*, 2015; Samykutty *et al.*, 2013). It has been observed that piperine can terminate the replication, and thereby leads to cell death in prostate and colon and cancer cells (Ba *et al.*, 2018; Yaffe *et al.*, 2013). In case of triple-negative breast cancer (TNBC) which is a very aggressive type of cancer, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) based therapies, are most effective. *In vitro* and *in vivo* studies with TNBC cells, indicate that piperine is an efficient adjuvant to enhance the efficacy of such therapy as it mediates the inhibition of p65 phosphorylation and survivin, a requirement for tumour progression (Abdelhamed *et al.*, 2015). Further, Damanhouri and Ahmad (2014) have suggested that inspite of the piperine's cytotoxic action on cancerous cells, its effect on healthy cells remains unaffected, hence its potential as an alternative therapy.

The array of phytochemicals in pepper contribute to reversing the multidrug resistance cells especially in sarcoma which derails management and therapy (Manayi *et al.*, 2018).

3.4 Anti-inflammatory

Inflammation is a fundamental factor in body's defense system and chronic inflammation outlines multiple conditions, including cardiovascular disorders, arthritis, diabetes, chronic infections and cancer. Several laboratory studies suggest that piperine, the key active composite in black pepper may efficiently brawl inflammation (Kunnumakkara and Sailo, 2018). In animal models, wherein arthritis is induced by collagen, piperine reduces inflammation, ameliorates oxidative stress and inflammatory blood markers along with positive impact on improving the histology. Similarly in asthma and chronic allergies, wherein inflammation of airways results, piperine has helped limit the same. The synthesis of prostaglandin E2, expression of interleukin 6 and matrix metallo-proteinase is inhibited (Umar *et al.*, 2018). The intensity of edema in animal models along with inhibition of the infilteration of eosinophils too was reported. This can be attributed to the suppression of T cell activity and the Th_2 cytokine production (Aswar *et al.*, 2015).

As per a study by Takoori *et al.* (2019), amongst the constituents with potential of being anti-inflammtory, most prominent are piperine, piperic acid, piperamide, piperlonguminine, piperolein-B, piperitine, pellitorine and eugenol.

3.5 Hypolipedemic

Obesity and hyperlipidemia are known risk factors for cardiovascular disorders as well as fatality (Reiner, 2017). Extracts of black pepper extract in rats induced with rich fat diet, affects cholesterol uptake by reducing the cholesterol transporters as these are internalized in presence of the same (Parim *et al.*, 2015). Pepper facilitates the enzymatic breakdown of fats, thereby preventing the buildup of fats in the body and it also enhances the assimilation of factors with the potential to lower cholesterol (Embuscado, 2019). Piperine down regulates the transcription of major adipogenic factors, namely; peroxisome proliferator-activated receptor-γ (PPARγ), sterol regulatory element-binding transcription factor (SREBP-1c), and CCAAT-enhancer-binding proteins (C/EBPβ), thereby diminishing the fat cell differentiation. Further, the regulation of modifications in the histone proteins regulates the expression of lipolytic and adipogenic genes, suppressing adipocyte differentiation. This holds immense application as a prospective option for treating obesity and related disorders (Park *et al.*, 2019).

Yafang *et al.* (2020) found that in mice who were fed a high fat diet, piperine regulates the adipose tissue expansion related genes (ATE), improvising the metabolism of lipids and protecting against obesity. It was observed that the regulatory effect on lipolytic and lipogenic genes, is more pronounced in visceral rather than subcutaneous fat.

3.6 Antimicrobial

The antimicrobial activity of pepper and its phytoconstituents have been extensively studied and found effective against multiple organisms. It also has potential as an antifungal against *C. albicans* as suggested by Aldaly (2010). Piperine and its derivatives are largely electronegative with an ester group, a carboxy group in the side chain and lack unsaturation, and the same has been associated with providing antibacterial properties.

Alencar and Castro (2017), suggested that pepper has activity against the promastigote forms, thereby can be used as anti-leishmanial. Amperayani *et al.* (2018) synthesized piperine derivatives with pyridine scaffold and noted antimicrobial activity against *Streptobacillus* sp., *B. subtilis*, *E. coli*, *S.aureus*, *S.typhi*, *A.niger*, *A. flavus*, and *A. fumigatus*. Combination therapy with ciprofloxacin and piperine lead to enhanced antimicrobial activity against *E. coli* and *B. subtilis* (Maitra, 2018).

Besides its pharmacological use as an antimicrobial, food sciences too has explored the use of this spice.

Studies report its efficacy as a microbiological preservation against broad microbial load (Krumov *et al.*, 2010), in fermented sausages against *L. monocytogenes* (Martínez *et al.*, 2010) and *S. aureus* in cheese (Krumov *et al.*, 2010). Its use in food preservation can be attributed to dropping down the oxidation of lipids (Martínez *et al.*, 2007).

3.7 Other pharmacological uses

SK-N-SH cells were subjected to rotenone-induced neurotoxicity, wherein treatment with piperine lead to restoration of mitochondrial function leading to an increase in viability of cells. It was observed that in case of Parkinson's disease model, it activates protein phosphatase 2A and inhibits mTORC1, providing neuroprotection (Liu *et al.*, 2016). It is not only in animal models, but even chemicals induce neurotoxicity and piperine offers protective effects when the same in accelerated in presence of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and corticosterone (Singh *et al.*, 2017).

Amongst many properties associated with pepper, studies to prove its analgesic property are multiple. In acetic acid, induced writhing, administration of piperine intra-peritoneally increases the rejection time in the tail flick assay, mediated *via* opioid pathway. Thus, it inhibits secretion of inflammatory cytokines, synthesis of prostaglandin E2 and stimulation of calcium influx (Mahboubi 2021; Pal and Joshi, 2020).

Over the years pepper has been used for issues associated with the gastrointestinal tract. Pepper has been found to cause saliva reflex flow, leading to an increase in gastric juice secretion thereby increasing the appetite. With appetite being enhanced, the gastro-intestinal movements are augmented, with consequent eructation of gas and relief of colic (Meghwal and Goswami, 2012).

In alloxan-induced diabetic mice, Atal *et al.* (2012) studied piperine's effect on blood glucose level. On administering piperine at different concentrations, (5, 10 and 20 mg), they observed significant antihyperglycemic activity. Studies on using pepper with glimepiride enhanced the bioavailability of glimepiride as CYP2C9 enzyme is inhibited, suggestive that not only is piperine itself anti-diabetic but can also be a potential adjuvant (Veeresham, *et al.*, 2012). Mehrotra *et al.*, (2019) studied the α-glucosidase as well as the α-amylase inhibitory activity of hydroacetone pepper extracts and found it to be effective with an IC_{50} value of 269.9 and 573.2 µg/ ml for α-glucosidase and α-amylase, respectively. Thus, it can be used towards managing hyperglycemia.

4. *Cuminum cyminum* L. (cumin)

Cumin or jeera is one of the most popular culinary spices in cuisines, especially in the Asian subcontinent. It is a member of the Apiaceae family with a spicy sweet and peppery flavor. Cumin is native from the East Mediterranean and South Asia, though now it is cultivated across the world, with the largest producer and consumer being India. Amongst, the prominent producers are Syria, Turkey, Iran, Indonesia, Sudan, Egypt, Morocco, Algeria, and Libya (Gondalia *et al.*, 2019).

Cumin seeds are rich in monounsaturated fats, protein, dietary fiber along with vitamin B, vitamin E and many dietary minerals. The nutritional value is depicted in Table 5 (Shamina Azeez, 2012).

The distinctive flavorand aroma of cumin is due to the essential oil content. The main constituents of the oil are the aldehydes, *viz.*, cumin aldehyde, p-mentha 3-en-7-ol and p-mentha 1, 3-dien-7-ol, and the main constituents are depicted in Table 6 and Figure 3 (Rana, 2014).

Table 5: Nutritional composition of black pepper per 100 g

Constituents	Composition
Food energy	375 (Kcal)
Water	8.0 (g)
Carbohydrates	44.0 (g)
Protein	18.0 (g)
Fat	22 (g)
Calcium	931 (mg)
Magnesium	366.0 (mg)
Phosphorus	499.0 (mg)
Sodium	168.0 (mg)
Potassium	1788.0 (mg)
Iron	66.0 (mg)
Zinc	5.0 (mg)
Thiamine	0.07 (mg)
Riboflavin	0.210 (mg)
Niacin	0.8 (mg)
Ash	8.0 (g)

Table 6: Average composition of volatile compounds in cumin

Compound	Composition (%)
Cuminaldehyde	49.4
p-cymene	17.4
α-terpinen-7-al	6.8
β-pinene	6.3
γ-terpinene	6.1
p-cymen-7-ol	4.6
Thymol	2.8
α-pinene	0.4
p-cymene-8-ol	0.4
Carvacrol	0.4
Limonene	0.3
Myrcene	0.3
Terpinen-4-ol	0.3
α-Thujene	0.2
m-cymenene	0.2
α-terpineol	0.2

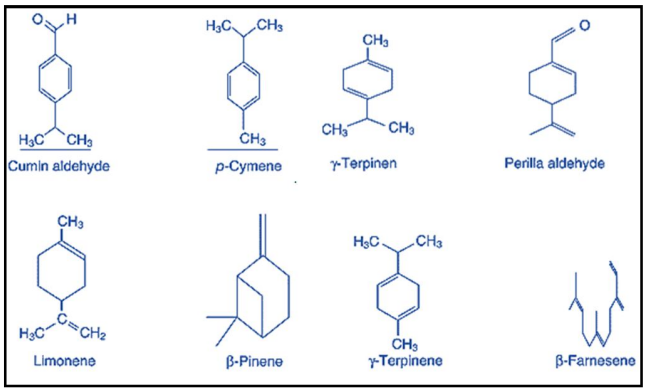

Figure 3: Structure of prominent constituents of cumin.

4.1 Antioxidant

One of the most favored methods to study the antioxidant activity is the use of DPPH radical scavenging assay and comparison with synthetic antioxidants as BHT and BHA. The cumin oil has shown to possess higher antioxidant activity and the activity is dose dependent. 50% DPPH radicals/ml were scavenged at 5.4 µg concentration (Allahghadri *et al.*, 2010). The oils of cumin extracted in hexane, showed linoleic acid was the dominant fatty acid with 89.70 mg kg^{-1}, α-tocopherol content, thereby providing good antioxidative potential (Hosseini *et al*, 2020).

An 80% methanolic extract *C.cyminum* of depicted, IC_{50} value of 1.641 mg. The phytochemicals in the extract, namely; flavonoids, alkaloids, phenol, terpenoids, saponins, and steroids were found to be responsible for the antioxidant property (Prajapati *et al.*, 2019).

In animal models, lipid peroxidation was evaluated using thiobarbituric acid reactive substances (TBARS) assay. The cumin extract significantly inhibited lipid peroxidation, on comparison with the golden standard ascorbic acid (Koppula and Choi, 2011).

4.2 Immunomodulatory, anti-inflammatory and analgesic

Multiple models can be used to study anti-inflammatory and analgesic effects, amongst which the popular ones are carrageenan-induced paw oedema, cotton-pellet granuloma, acetic-acid induced writhing and hot plate. An aqueous cumin extract depicts substantial analgesic activity in acetic acid induced writhing while the ethanolic extract (200 and 500 mg/kg), showed effectiveness in hot plate method, while both were effective in the other two models (Bhat *et al.*, 2014).

Wei *et al.* (2015) investigated the anti-inflammatory effects of cumin on RAW 264.7 cells stimulated with lipopolysaccharide (LPS). The expression of inducible nitric oxide synthase, COX-2, IL-6 and IL-1 were significantly inhibited using real-time PCR tests. The phosphorylation of c-Jun N-terminal kinase and extracellular signal regulated kinase (ERK) were studied using western blotting analysis and the same were found to be inhibited. Also, the transcription of nuclear factor-kappa B (NF-κB), induced by LPS was blocked.

The enzyme kinetics was studied for inhibition of lipoxygenase activity, using a methanolic extract of *C. cyminum* which lead to the discovery that the inhibitor is basically cumin aldehyde which acts as a competitive inhibitor with IC50 as 1.370 μM (Tomy *et al.*, 2015). The anti-inflammatory property of cumin aldehyde has been devoted to its ability to inhibit mitogen activated protein kinases and NF-κB in LPS-stimulated RAW cells (Srinivasan *et al.* 2018).

Johari (2011) evaluated the role of cumin in the immune system and suggested that it causes a significant role in activating both Tc and Th cells and leads to increase in the Th_1 cytokine levels in both normal as well as immunosuppressed animal models. In restraint stress induced immune-suppressed animals, it has been suggested that *C. cyminum* counters the depletion of T lymphocytes, as it decreases the raised levels of corticosterone as well as the increase of size of adrenal glands, thymus, and spleen (Boskabad *et al.*, 2005). Cumin aldehyde has been found to attenuate nociceptive and neuropathic pains. The antinociceptive effect is mediated through cuminaldehyde and the opioid receptors are implicated through the L-Arg/NO/cGMP pathway. Thus, it was observed by Koohsari *et al.* (2020) that cumin relieves pain mainly due to its ability to suppress cytokines involved in inflammation.

4.3 Antimicrobial and antifungal

The utility of *C. cyminum* essential oil for its antimicrobial activity has been observed against most common causative agents, *viz.*, *S. aureus, L. monocytogenes* and *E. coli*, wherein death time post exposure to the oil was studied. Complete death time on exposure to *C. cyminum* oil was 180, 90, and 20 min (Fakoor and Rasooli, 2008). Investigation into the minimum inhibitory concentration against *S. aureus, B. cereus, E.coli* O157:H7, *S. enteritidis* and *L. monocytogenes*) were in the range of 0.37-3.0 mg/ml (Oroojalian *et al.*, 2010).

The study on antifungal effect of cumin essential oil in *Fusarium verticillioides* strains using RT-PCR analyses, deduced that the oil caused reduction in the expression of FUM1 gene (Khosravi *et al.*, 2015). The spice also possess antiviral activity as evident against herpes simplex virus 1, wherein significant activity was found at 1000 μg concentration using cytopathic assay (Romeilah *et al.*, 2010).

Hu *et al.* (2008), proved that cumin extract was effective as a fungicide against *A. alternata, A. solani, B. graminis* and *B. cinerea, G.graminis, P. capsici, R. cerealis , S. sclerotiorum, T. cucumeris, V. dahliae*, due to the presence of p-isopropyl benzoic acid and p-isopropyl benzaldehyde. The *in vitro* antifungal activities of *C. cyminum* oil was observed for many pathogenic *Candida* species, with effectivity being maximum for *C. albicans* and *C. dubliniensis* in terms of minimal inhibitory concentration (MIC).

C. cyminum oil has many phenolic compounds with the potential to inhibit fungal enzymes like pectinase, responsible for hydrolyzing the fruit cell wall, and thereby invading fungal infections (Abdul-Jabbar, 2017).

Constituents in cumin essential oil inhibit to the tune of 63%, the b-carotene bleaching *via* hydroperoxides neutralization. If this reaction is permitted, it can lead to oxidation of highly unsaturated β-carotene. This leads to antimicrobial effects and electron micrographs suggest that the cell permeability is increased, rupturing membrane (Alizadeh *et al.*, 2019)

4.4 Anticarcinogenic

Research on use of cumin for its antineoplastic effects have shown its significant potential for therapeutic use. The inhibitory effects of cumin aldehyde on melanin synthesis was studied and it was observed by Nitoda and Fan (2008) that at low concentrations, inhibition was observed in mouse melanoma cell while high concentration was required for human cell lines. Tsai *et al.* (2016) delineated that cumin aldehyde triggers caspases 3 and 9, considered pro-apoptotic proteins that alter mitochondrial integrity. They inhibit the synthesis of *topoisomerase* I and II, which are required for maintaining DNA integrity, and thus enhance apoptosis along with increased leaching of cytochrome c and increased lactate *dehydrogenase* activity. These observations were noted only in human colorectal adeno carcinoma cells, but also *in vivo* in colorectal cancer mouse model, wherein a reduction in tumor size was observed due to aptoptosis induced in presence of cumin aldehyde. In human lung squamous cell carcinoma NCI-H520 cells, cumin extracts stimulated apoptosis by increased expression of pro-apoptic bax and bac genes along with a decrease in the expression of apoptosis suppressing factors bcl-XL and bcl-2 (Yang *et al.*, 2016). Cumin aldehyde in cumin is the most effective component in preventing α-SN fibrillation and has no effect on disaggregating preformed fibrils. Due to a Schiff base reaction between amine groups and its aldehyde group, cumin aldehyde prevents formation of β-structural fibrils. An advantage of its use is that it proved to be non-cytotoxic on PC12 cells as per MTT cytotoxicity assays (Morshedi *et al.*, 2015).

Using purified fractions of cumin extract in ethanol and hexane, amongst the flavones, luteolin-7-O-glucoside proved to have best potential for anticancer activities. In MCF-7 cell line, the selectivity index was observed to be 8.0 with IC_{50} value as 3.98 μg/ml. Thus, this component in cumin can also play role for its significant cytotoxic effect as a chemopreventive drug and its chemotherapeutic effects too can be studied (Goodarzi *et al.*, 2020).

4.5 Antidiabetic and hypolipidemic

The plants produce many secondary metabolites as alkaloids, terpenoids, flavonoids, and polysaccharides and these have anti-

diabetic activity. These compounds help in inhibiting carbohydrate metabolic enzymes as alpha-amylase, and alpha-glucosidase, promote glycogenesis, stimulate B-cells for insulin secretion, protect damage of B-cells, and promote peripheral tissues to increase glucose uptake (Chen *et al*., 2015; Gaikwad *et al.*, 2014; Putta, *et al.*, 2016; Zheng, *et al.*, 2019; Mehrotra *et al*., 2019).

A fallout of diabetes is the increase in activity of aldol reductase due to polyol pathway activation which triggers secondary complications in diabetes. Cumin has been found to reduce intracellular sorbitol accumulation, and thus be effective as an antidiabetic (Saraswat *et al.*, 2008).

In diabetes type II patients on cumin supplementation, a decrease in serum insulin, FBS, and Hb1Ac was observed. Increase in serum adiponectin, which is associated with inflammatory indices of TNF-α and hsCRP was also observed (Jafari, *et al.*, 2017). Hemlata *et al.* (2019), has reported *in vitro* anti-amylase activity in cumin along with 18 other dietary spices. In streptozotocin-induced diabetic rats, *C. cyminum* seed extracts improved glucose tolerance with a significant fall in blood glucose levels, as it inhibited α-glucosidase and aldose reductase. At the onset of diet dependent diabetic distress, the supplementation with cumin can potentially relieve the protein and amino acid catabolic rate, alleviate the anaerobic redox burden, and eases nephron permeability (Kannan *et al.*, 2019).

Cumin also possess antidyslipidemic activity as it reduced serum triglycerides, total serum cholesterol, serum LDL-C, with an increase in serum HDL-C, in Syrian golden hamster put on a high fat diet (Srivsatava *et al.*, 2011). Due to its antioxidant potential, cumin phytochemicals have the potential to modify paraoxanase 1activity, known in human atherosclerotic lesions to protect against the plasma lipoproteins oxidation by hydrolyzing lipid peroxides, and oxidizing the low density lipoprotein (LDL). Samani and Farrokhi (2014) found a significant decrease in the level of LDL with an increase in paraoxonase and arylesterase activities. Supplementation of orlistat 120 with cumin seeds resulted in a significant weight loss, lowering of BMI along with significant serum insulin levels reduction (Taghizadeh *et al.*, 2015). In adipocytes, cumin aldehyde reduces the other triglycerides and cholesterol as well as glucose uptake.The adipocytes that mature in the presence of the phytochemical, have reduced expression (i) adipocyte-specific transcripts, (ii) binding protein to CAAT-enhancer and (iii) peroxisome proliferator-activated receptor gamma genes (Mohammad, 2020).

4.6 Other pharmacological uses

Cumin has been an integral part of major cuisines. The stomach of rats when perfused with aqueous extracts of cumin increased the stomach acid secretion (Vasudevan *et al.*, 2000). Milan *et al.* (2008) reported secretion of protease, amylase, lipase and phytase activities, on cumin consumption.

Analgesics as diclofenac leads to ulcerations. Use of cumin extracts, accelerated the healing from the ulcers and increased the regeneration of gastric mucin which provides protection against ulcers (Pratyusha *et al.*, 2013). In castor oil induced diarrhea in rats, the effect of aqueous extract of cumin was studied. The extract significantly inhibited the defecation time delaying, the frequency of diarrhea, intestinal propulsion and secretion of intestinal fluid in a dose dependent manner (Sahoo *et al.*, 2014). Through, *in silico* studies, cumin has proved to be an excellent target for diarrhea therapy (Behera and Bhadra, 2020).

Anti-osteoporotic property of cumin was evaluated in bilaterally ovariectomized rats. The intake of cumin significantly reduced the excretion of urinary calcium, and thus significantly increased the mechanical strength of bones as the calcium content increased. The gain in body weight and atrophic uterus weight remained unaffected, thus preventing ovariectomy-induced bone loss without any anabolic effect (Shirke *et al.*, 2018).

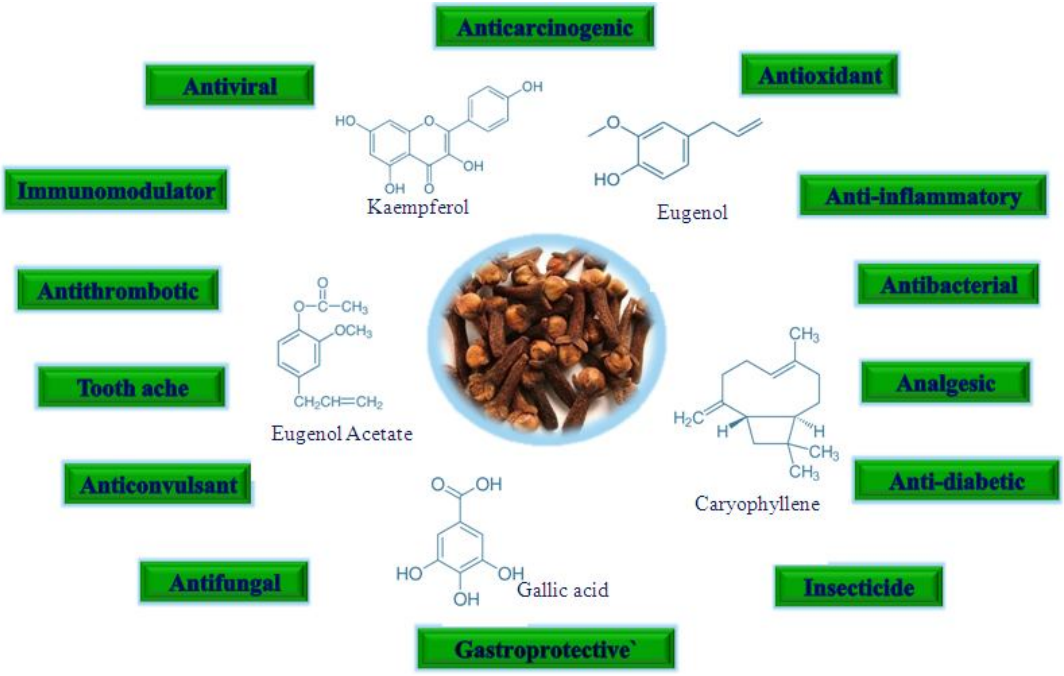

Figure 4: Summary of pharmacological properties of *S.aromaticum*.

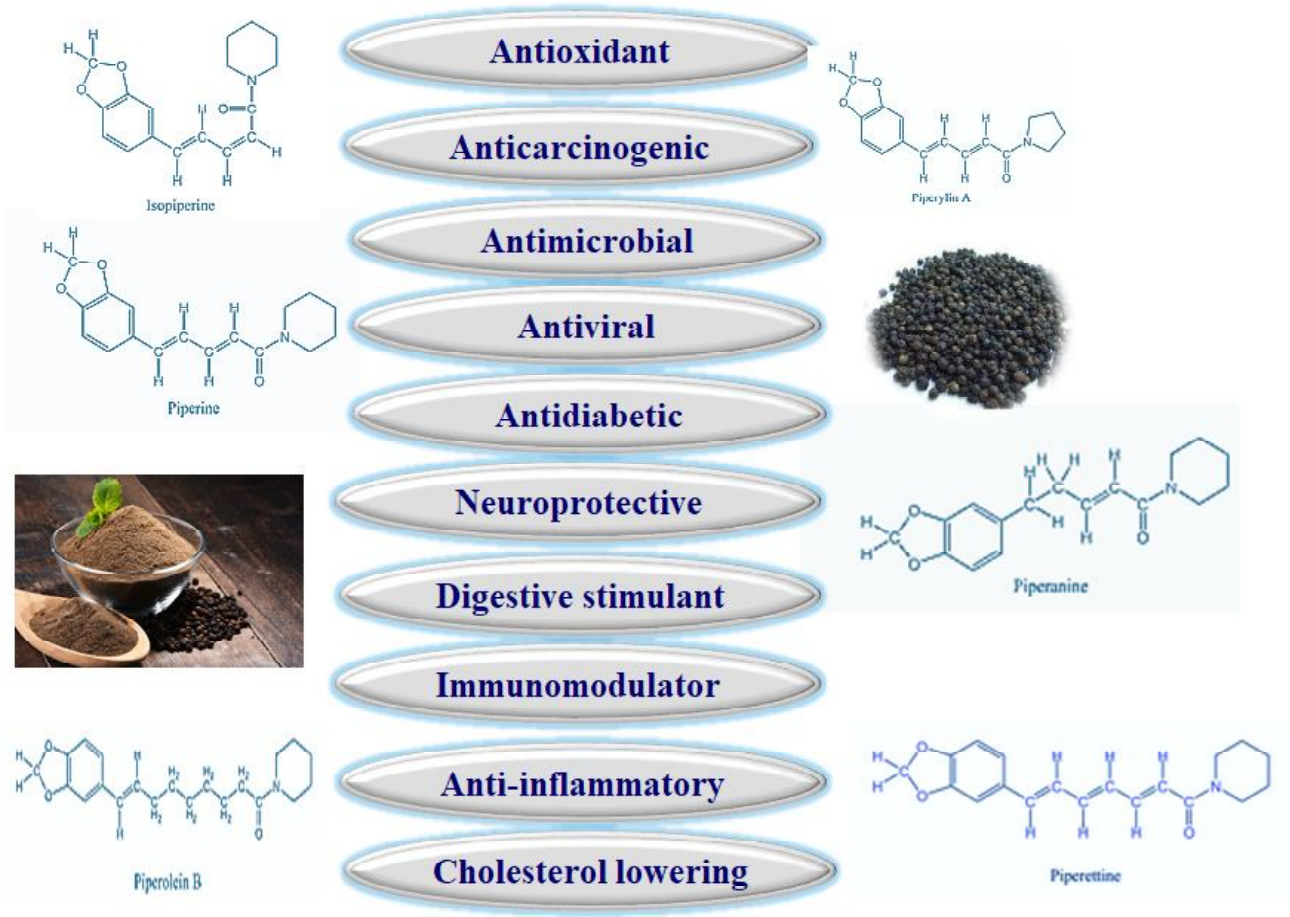

Figure 5: Summary of pharmacological properties of *P. nigrum*.

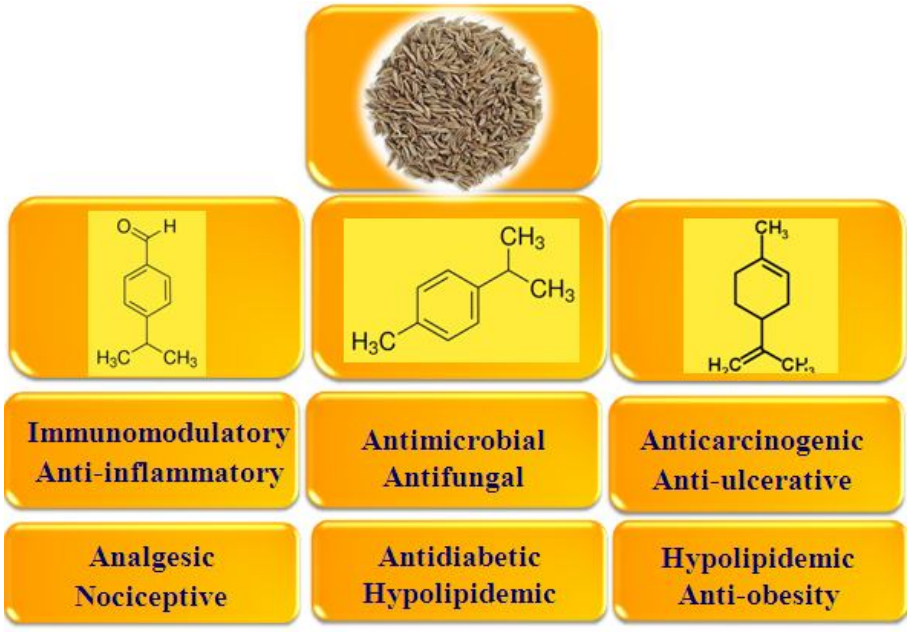

Figure 6: Summary of pharmacological properties of *C. cyminum*.

5. Conclusion

The use of herbs and spices has been employed in traditional practices and is a way of health in large part of the globe. To give an impetus to their use, efforts are being made by researchers to identify the bioactive compounds in herbs and spices and to understand their role in health promotion. The reviewed spices have multiple uses for various health concerns which are manifested due to a plethora of active phytochemicals in the spices. Figures 4-6 represent a summary of their pharmacological properties. The chemical structure of each such phytochemical provides it the potential to mediate wellbeing. The concentration of phytochemicals in the plants/herbs/spices is dependent on the season, the plant cultivar, the soil condition along with the supply of nutrients. The need of the hour is the conduct of multiple studies to provide strong evidence for underlining the mechanism for their action and optimization of the dosage. Another important aspect to be considered is the use of allopathic medicines along with the herbal regime. Sufficient research evidence suggests that herb-drug interactions exist and can be fatal. The natures pharmacy is diverse, and available for all, with due precautions which can be mitigated with efforts to study these herbal medicines and their modus operandi in detail.

6. Future prospects

The increased interest in the use of plant-based traditional medicines and herbal remedies, comes with a rider. It requires that the users be made aware on the safety, quality as well as the use of these herbs and spices. Quality assurance and quality control are the need of the hour as these herbal remedies are largely grown and harvested as wild type, where natural as well as extrinsic factors control the yield of phytochemical constituents. Plant material is likely to have varying concentrations of active compounds and as concentration plays a role in efficacy, the same is likely to be affected. Currently, most herbal preparations are prepared without the legal requirement of stringent quality control and quality assurance. Thus, the quality of such remedies is often compromised for the presence of either natural or anthropogenic contaminants effectively leading to adverse reactions which may turn to be fatal. The governing authorities should lay stringent legal norms alike the allopathic medicines for quality control of not only the final product but also the raw material. This will facilitate the use of herbs that heal to provide health benefits to human race.

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Conflict of interest

The author declares that there are no conflicts of interest relevant to this article.

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