

Traditional and Novel Herbal Drugs Emerging as Potent Novel Combinations for Managing Morbidities by Pharmacological and Mechanistic Studies

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Abstract

Background: Herbal drugs are used in treatment of diseases since decades. Major contributing factor for their use is easy availability, less expensive and more belief of common population because of relatively less side effects compared to allopathic medicines. Medicines of natural origin or functional foods in the prevention of disease are the need of hour. Hence, the present review focused on activity of four drugs viz. *Withania somnifera*, *Allium sativum*, *Curcuma longa* and *Azadirachta indica* and role in different clinical complications.

Methods: A thorough review of all the articles, research as well as reviews available regarding the concerned topic was performed. MEDLINE database was searched and English language articles were preferably selected.

Results: *Withania somnifera*, *Allium sativum*, *Curcuma longa* and *Azadirachta indica* have shown alleviation in inflammation, diabetes and cancer states. The herbal drugs have shown beneficial effects in the prevention and treatment of these disorders.

Conclusion from these facts: Utilizing this concept, it can be assumed that herbal drugs play an intricate role in safeguarding the health of individuals from life-threatening complications. However, validation and reproducibility

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of results in clinical trails should be there in order to confirm the safety and efficacy of these herbal drugs.

Keywords: Herbal plants; *Withania somnifera*; *Alium sativum*; *Curcuma longa*; *Azadirachta indica*

1. INTRODUCTION

Herbal Plants as Therapeutic Agents: Herbal plants have been used in the mitigation and prevention of diseases from prehistoric times. With the advent of civilization and increase of population, the popularity of herbal drugs is also increasing. This can be ascribed because of the increased costs associated with allopathic medicines. Moreover, the fear of side effects and long term adherence to these medications also obscure their use. Traditional herbal drugs are associated with historical and cultural beliefs and has attributed widely to their use in the modern world. The existence of word “herb” comes from Latin word “herba” and French word “herbe”. In the modern world, herb refers to plant part namely fruit, seed, stem, bark, flower, leaf, stigma along with the non-woody part from trees and shrubs.

Some primary diseases arise spontaneously such as, diabetes mellitus (DM), cancer, thyroid, inflammatory disorders, depression, cardiovascular diseases and arthritis, Figure 1. Management of these diseases are very important otherwise the consequent outcomes could be more complicated and dangerous. Herbal medicines that are mentioned in the present article may help in disease management and therapy. Diabetes mellitus continuously increasing day by day worldwide, according to International Diabetes Federation in 2017 an estimated 425 million adults, a total that is set to reach 629 million by 2045 (IDF, 2018). Similarly, cancer and thyroid are also leading enormously. In 2012, according to Cancer Research UK, an estimated 14.1 million new cases of cancer developed worldwide (Cancer Research UK, 2018). According to various studies on thyroid disease, it has been predicted that about 42 million people suffer from thyroid diseases in India (Indian Academy of Sciences, 2011). Depression and cardiovascular disease have become the leading cause of mortality in India, due to the different lifestyle (Srinath *et al.*, 2005). Arthritis is an autoimmune inflammatory disease that affects the joints and surrounding tissues. According to World Health Organization (WHO) have symptomatic osteoarthritis aged over 60 years and about 9.6% of men and 18.0% of women suffered worldwide (Rachel *et al.*, 2013). Therefore, it is important to take care of these diseases properly. Herbal medicines could be a better option for management of the disease, herbal medicines may use with combinational therapy. So, this is a high time to know about herbal compounds and find

better new options. The present review describes anti-inflammatory, anti-diabetic, anti-cancer, anti-anxiety, cardioprotective and anti-thyroid disease of four drugs viz. *Withania somnifera*, *Allium sativum*, *Curcuma longa* and *Azadirachta indica*. Overall representation and involvement of these herbal drugs in different medical complications are mentioned in Figure 1.

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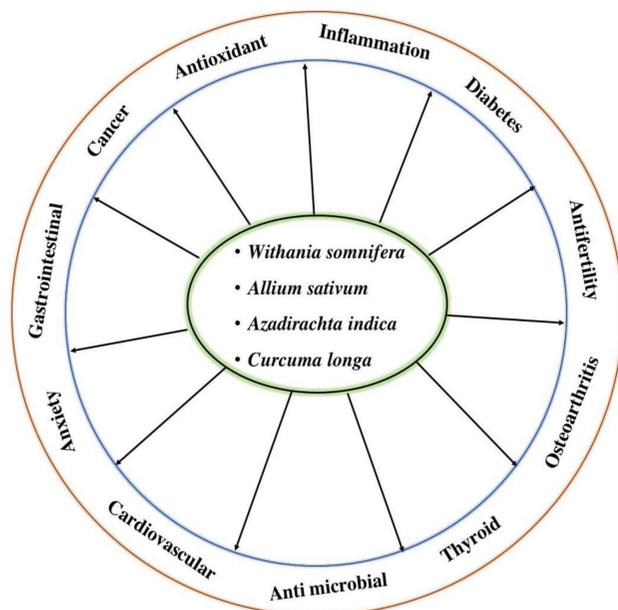


Figure 1: Wheel depicting the use of herbal medicines rejuvenation of different medical complications.

2. HERBAL PLANTS: USE IN INDIA AND IN GLOBE

Plants came in existence even before human existence. Natural resources of a country are of utmost importance as they sustain country's economy and health. In view of this reason, the use of traditional herbs in attenuation of diseases have attracted attention of many researchers not only in India but also across the globe. Data from World Health Organization (WHO), reports the increased use of traditional medicine in India and in other parts of world. India has a rich wealth of traditional medicine and around 65% population of rural area use herbal medicines for their primary health care. Furthermore, in China the use of traditional medicine is approximately 40% and in Colombia and Chile the use reported is about 40% and 71% respectively. The use of alternative

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or complimentary medicines in developed countries is also common (WHO, 2003). The market of herbal medicines in India is worth ~US \$1 billion while its cost globally is around US \$62 billion, with the Chinese herbal medical market about ~ US \$19 billion (Aneesh *et al.*, 2009).

The strategy for use of traditional medicines was made by WHO in the year 2014. This strategy promotes the safe and effective use of traditional medicines by regulating research and integrating products which play an intricate role in mobilizing the health and wellness of mankind (WHO, 2014).

3. WITHANIA SOMNIFARIA

Withania somnifaria, commonly known as ashwagandha or winter cherry plays multifarious role in morbid conditions. It derives its name because of smell of its herb like that of horse and post consumption derivation of strength similar to horse. The growth of *Withania somnifera* is best in rainy-season and it attains maturation in relatively dry season. The plant can tolerate a temperature range of 20-38 °C and can withstand to a temperature even as low as 10 °C. The flowers of the plant are small and green in growing stage, while in ripening stage it becomes orange-red and has elicited milky properties. The flower, leaf and tuberous roots of *Withania somnifera* have been used for medicinal purposes. It serves as an ingredient in many formulations approved for a variety of clinical conditions (Chatterjee *et al.*, 1995). The astounding role of *Withania somnifera* in treatment of so many vivid health disorders, like diabetes (Andallu *et al.*, 2000), cancer (Rai *et al.*, 2016) and inflammation has made it an important therapeutic component in the modern world (Sangita *et al.*, 2012). Another study conducted by Gorelick *et al.*, 2015 has shown the increase in uptake of glucose in myotubes and adipocytes by leaf and root extract of *Withania somnifera* (Gorelick *et al.*, 2015). Also, in another study the polyherbal formulation containing *Withania somnifera* as one of the component has shown anti-diabetic effect in streptozotocin induced diabetes in rats (Gautam and Kalia, 2013).

3.1 Anti-inflammatory Activity

The utility of ashwagandha in immunoregulating and anti inflammatory properties have been studied. The entry of pathogen inside the body or traumatic condition leads to infection which intensifies inflammatory processes by innate and adaptive immunity. This consequently alleviates blood pressure and stimulates organ damage (Agita *et al.*, 2017). Studies also reported the inhibition of protein denaturation and prevention of immunological damages by *Withania somnifera* (Gorelick *et al.*, 2015). Study conducted by Gupta *et*

al., 2014 showed anti-inflammatory and antioxidant property of root powder of *Withania somnifera* in collagen-induced arthritic rats (Agita *et al.*, 2017).

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3.2 Anti-Diabetic Activity

Diabetes mellitus is a convoluted endocrine and metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. It is broadly classified into two types, namely- Type-I Insulin dependent diabetes mellitus (IDDM) and Type-II diabetes mellitus which is also known as non-Insulin dependent diabetes mellitus (NIDDM). The former condition is characterized by destruction of pancreatic beta cells that leads to insufficient insulin production and in latter condition insulin resistance occurs (Kalinowska *et al.*, 2017). Study conducted by Andallu *et al.*, 2000 reported hypoglycemic, diuretic and hypocholesterolemic properties of *Withania somnifera* root powder (Andallu *et al.*, 2000).

3.3 Anti-Cancer Activity

The cells perform specific function of division or proliferation according to requirements of body. The abnormal proliferation of the cells leads to development of cancer which has emerged as harbinger to number of complications. The prevalence of cancer is increasing at an alarming rate and requires utmost attention of researchers in development of therapy which should be devoid of side effects. Also, the current available therapies have shown many impairments in form of side effects. *Withania somnifera*, a medicinal herb has exhibited significant anticancer activity against cancer cells. The root part of *Withania somnifera* has shown anti-cancer activity (Rai *et al.*, 2016). Another study conducted with *Withania Somnifera* root, stem and leaves has shown *in vitro* anticancer activity against various human cancer cell lines (Yadav *et al.*, 2010). Recent study conducted by Setty *et al.*, on prostate cancer, shows the targeting of interleukin-8 (IL-8) and cyclooxygenase-2 (COX-2) by *Withania somnifera* leading to impairment in cancer progression (Setty *et al.*, 2017).

3.4 Anxiety and Depression

Withania somnifera also have anxiolytic and antidepressive action in animals. Lakshmi *et al* 2010 shows comparative study for anti-stress activity with *Withania somnifera* formulation in mice. Oral dose was given to mice for seven days and significant anti-stress activity was measured by swimming endurance test (Grandhi *et al.*, 1994). *Withania somnifera* roots extract have been investigated against a rat model of chronic stress (CS). Chronic stress induced significant

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symptoms of hyperglycemia, immunosuppression and mental depression, gastric ulcerations. These CS induced perturbations were brought down by *Withania somnifera* formulation (Bhattacharya and Muruganandam, 2003).

3.5 Cardiovascular Protection

Withania somnifera have shown protective action in cardiovascular system against myocardial infarction, stroke and other peripheral vascular disease. Cardiovascular is a most frequent causes of cripple disease and death. Myocardial infarction may interrupt the blood supply and then subsequent damage induced by reperfusion (Kalogeris *et al.*, 2012). Cardiovascular disease may cause by so many metabolically and physiological parameters of the body, *Withania somnifera* root extract are effective on hypoglycemia, diuretic, and hypocholesterolemic conditions. One one of the study was performed by Andallu and Radhika, on six type2 diabetes mellitus subjects and six mildly hypercholesterolemic subjects were treated with the *Withania somnifera* powder extract and got effective result (Andallu and Radhika, 2000). Increase production of Reacting Oxygen Species also implicated in the pathology of cardiovascular disease. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a transcriptional regulator of phase II antioxidant enzymes. Activation of Nrf2 has been suggested to be imperative role in attenuating oxidative stress associated with Cardiovascular disease. *Withania somnifera* along with combination of five other herbal plant source effective on activation of Nrf2, therefore upregulation of phase II enzyme Nrf2 protect cardiomyocytes against Oxidative stress (Reuland *et al.*, 2012).

3.6 Anti-Thyroid Activity

Dysfunction of hypothalamic-pituitary-thyroid neuroendocrine cause the bipolar disorder. This thyroid dysfunction has been associated with shift of metabolic and cognitive function (Hendrick *et al.*, 1998). *Withania somnifera* also associated with thyrotoxicosis, and administered to the mice shows significantly elevated level of thyroxine (Gannon *et al.*, 2014). Four subjects were treated with *Withania somnifera* root extract (600 mg daily) which improved serum TSH, T3 and T4 level significantly as compared to placebo (Sharma *et al.*, 2017). Therefore, *Withania somnifera* could be a potential herbal medicine for better clinical outcomes.

4. ALLIUM SATIVUM

Allium sativum, also known as garlic has been in use from ancient time for folk medicine and in diet as a flavoring agent. Garlic attains importance not

only because of its use as vegetable but also as a therapeutic and medicinal component in both traditional and modern medicine. Garlic also contains some bioactive compounds among which sulfur-containing non-volatile amino acids (thiosulfinates), alliin or S-allyl-cysteine sulfoxide (ACSO) comprises the most predominant garlic flavor precursors (Hornickova *et al.*, 2010). Moreover, garlic also contains sulfur compounds which are basically responsible for educing it medicinal properties (Banerjee *et al.*, 2003). The enrichment of garlic with these components makes it an important therapeutic agent in the prevention and treatment of diseases like inflammation, diabetes and cancer.

4.1 Anti-inflammatory Activity

Garlic contains sulfur compounds which are of anti-inflammatory nature. Sulfur compounds inhibit the production of pro-inflammatory cytokines and nitric oxide (NO) (Hodge *et al.*, 2002). Study conducted by Lee *et al.*, 2012 have shown the anti-inflammatory properties of the four sulfur compounds extracted from garlic via hindering production of pro-inflammatory mediators NO and prostaglandin E2 (PGE2) (Lee *et al.*, 2012). Also, the leaves of garlic have shown inhibition of edema in experimental animals (Satarupa *et al.*, 2015).

4.2 Antibacterial Effect

Many herbal extracts or remedies have antibacterial activity. That is also a reason to use herbal products in dietary food. Garlic extract have antibacterial activity, inhibit the gram positive and gram negative bacterial growth. Garlic suspensions were extracted and tested at different concentrations and all of them showed an inhibitory effect against *Staphylococcus aureus* (Borek, 20016; Eltaweel, 2014). Another study conducted on clinical isolated *Staphylococcus aureus* and *Escherichia coli*. Antibacterial activity was performed by agar diffusion method (Debella, 2004)) with different concentration of garlic extract, and compared by the chloramphenicol and penicillin as a positive control and distilled water as negative control. Garlic extract showed antibacterial activity against both the microorganism (Abiy & Berhe, 2016). Multidrug resistance (MDR) bacteria is a major problem worldwide, most of primary antibiotics does not affect the bacterial growth. Garlic extract shows growth inhibition against the multidrug resistant methicillin resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis*. The *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis* were isolated from clinical patient and antibiotics susceptibility test were done by the disc diffusion method using Muller-Hinton agar medium. For same study was evaluate the antibacterial activity of garlic

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extraction. The efficacy of garlic extracts on *Staphylococcus aureus* ranging from (15-36) mm diameter zone of inhibition, while that of *Enterococcus faecalis* ranging from (14-33) mm diameter zone of inhibition (Janan *et al.*, 2016).

4.3 Anti-Diabetic Activity

Garlic is known as oldest cultivated plant world wide. Garlic supplement have shown a promising role in type-II diabetes mellitus (T2DM) management a promising role in type-II diabetes mellitus (T2DM) management Garlic has also shown to improve insulin sensitivity and the associated metabolic syndrome in animal models (Padiya *et al.*, 2011). Several studies conducted in the past reported increase in insulin production upon the supplementation of garlic. Garlic extract administrations orally show significant reduction in serum glucose, total cholesterol, uric acid, triglycerides, creatinine levels. Studies also observed increased level of serum insulin in diabetic rats but not in normal rats (Eidi *et al.*, 2006; Islam & Choi, 2008).

4.4 Anti-Cancer Activity

The use of herbal plants in treatment of cancer is in practice from decades Garlic have allicin and sulfur compounds, which have shown anti-cancer property (Carella *et al.*, 2001). Garlic used as a dietary supplement reduced the risk of cancer. Garlic extract shows. Researchers reported inhibitory effect on cancer (HeLa) cell line in a dose dependent manner by garlic extract and have also measured cytotoxicity effect on HeLa cells (Islam *et al.*, 2011). Another study conducted by Rajeev *et al.*, 2014 have investigated response of garlic extract on cell lines MCF-7 (Breast cancer), A549 (Lung cancer) and PA-1 (Ovary cancer) and has shown efficient cytotoxicity and growth inhibition (Rajeev *et al.*, 2014). Thus, garlic is still being used in India as well as globally for the treatment of numerous kinds of diseases, along with cancer as a natural herbal therapy.

4.5 Antioxidant Effect

Antioxidants are beneficial to the body and they protect from the harmful damage by free radicals. Increase level of free radicals can cause the damage and alter the cell death. Antioxidants may play a role in the prevention of some medical conditions, like cancers, arthritis-related conditions. Antioxidants used in food products can interact with free radicals, which helps in regulation of normal homeostasis. Antioxidant property of *Allium sativum* has been proved scientifically (Jackson *et al.*, 2002). Garlic extract acts as antioxidants to protect cells against reactive oxygen species (ROS) (Chung 2006). Compound

1,1-diphenyl-2-picrylhydrazyl (DPPH) present in garlic have radical scavenging activity (Querioz *et al.*, 2009) and superoxide dismutase activity in vitro (Jang *et al.*, 2008). Generation of reactive ROS by heavy metals, which initiates lipid peroxidation, through causing oxidative damage to critical macromolecules like DNA, proteins as well as cell damage (Das *et al.*, 2001).

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4.6 Cardiac Arrest Protection

Evidences have shown that *Allium sativum* has enormous potential in protection of cardiac arrest. *Allium sativum* derived compound such as ajoene have been demonstrated inhibition of platelet aggregation in animal model and reduction of platelet observed by thrombus formation dependent manner (Shah *et al.*, 2014) and augment the fibrinolytic activity (Sogani and Katoch 1981). Study has been performed by Benavides *et al* shows that vasoactive ability of garlic's sulfur compounds, where by red blood cells convert garlic's organic polysulphides into hydrogen sulphide, a known endogenous cardioprotective (Benavides *et al.*, 2007). In India, a study was conducted on 432 coronary artery patients and the patients were randomly divided into two groups and half of them were supplied with garlic juice in milk, and other group were not supplied with garlic juice. within the three years of the study time results showed nearly twice as many patients had died in the group in which garlic juice was not supplied (Yeh *et al.*, 2006). Garlic is well reported to scavenge oxidants, increase superoxide dismutase, catalase, glutathione peroxidase, inhibit lipid peroxidation as well as it reduces cholesterol synthesis (Borek, 2006).

5. CURCUMA LONGA

Curcuma longa, commonly known as turmeric is not only a spice. Its use as a medicinal herb is in practice from decades. It belongs to ginger family. It contains compounds called as curcuminoids among which the most applicable one is curcumin (diferuloyl methane). Other derived component from the plant are the flavonoid curcumin (diferuloyl methane) and various volatile oils containing tumerone, atlantone and zingiberone with some basic constituents like sugar, proteins and resins. The turmeric content in curcumin is not much high (4% by weight) (Nagpal and Sood, 2013) Curcumin attributed numerous therapeutic activities among which the most prominent ones are anti-carcinogenic, anti-diabetic and anti-inflammatory (Shehzad *et al.*, 2017).

5.1 Anti-Inflammatory Activity

The anti-inflammatory effect of *Curcuma longa* was attributed majorly due to curcumin acting through suppression of NF-kB and COX-2 activation (Julie

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et al., 2009). It also reduces the inflammation by lowering the histamine levels and increasing the production of adrenal glands. It attributes anti-inflammatory properties via inhibiting the biosynthesis of inflammatory prostaglandins from arachidonic acid and neutrophil function. Oral administration of curcumin in instances of acute inflammation was found to be equally effective as cortisone or phenylbutazone, and half effective in chronic inflammation (Shehzad *et al.*, 2017).

5.2 Anti-Diabetic Activity

As discussed in earlier section of this review, curcumin is having anti-inflammatory property which reduces the blood glucose level by suppressing inflammation due to hyperglycemia. This stimulates glucose uptake which up regulates GLUT2, GLUT3 and GLUT4 gene expression, consequently increasing insulin secretion from pancreatic tissue and decrease insulin resistance (Ghorbani *et al.*, 2014). A study report suggested that the administration of 0.5% of curcumin treatment in a diabetic model reduce the infiltration of macrophage in the kidneys of diabetic rats and suppressed the expression proinflammatory cytokine (TNF- α and IL- β). Curcumin has been reported to display protective effects against hyperalgesia in diabetic mice by inhibiting TNF- α release in dose dependent manner and reducing thermal sensation pain in the same (Mrudula *et al.*, 2017). It also activates adenosine monophosphate activated protein kinase (AMPK) which inhibits the accumulation of oxidative stress and lipid in kidneys (Ghorbani, et al. 2014).

5.3 Anti-Cancer Activity

Research done on curcumin in various carcinogenesis studies has shown its effect colorectal, breast, gastric, hepatic, and oral cancers (Julie *et al.*, 2009). Curcumin is a highly anti-inflammatory compound which acts by reacting with proinflammatory chemokines and cytokines. It actually a potential inhibitor of myeloid differentiation protein 2, alpha 1-acid glycoprotein, and various enzyme including histone acetyltransferase, cyclooxygenase (COX), inducible nitric oxide synthase (iNOS), human immunodeficiency virus type 1 protease and integrase, DNA methyltransferase and polymerase, protein kinases, focal adhesion kinase (FAK), protein kinase C (PKC) and phosphorylase-3 kinase. Curcumin is also capable to inhibit cytokinin like interleukins, IL-1, IL-2, IL-6, IL-8, IL-12, tumor necrosis factor alpha (TNF- α), mitogen activated protein kinase (MAPK), c-Jun N-terminal kinases (JNK), and can bind directly with DNA, RNA and proteins. Various transcription factors binds indirectly to curcumin including β -catenin, peroxisome, proliferator-activated receptor

gamma (PPAR γ) and signal transducer and activator of transcription (STAT) proteins (Shehzad *et al.*, 2010). Curcumin is also responsible to develop the expression levels of p53, reactive oxygen species (ROS) and p21, consequently decreasing the mitochondrial membrane potential (Goel and Aggarwal 2010). Furthermore, curcumin is highly potential and acts anti-carcinogenic by inhibiting several molecular beaten ups including inhibition of NF-kB and COX-2 (increased levels of COX-2 are associated with many cancer types); inhibition of arachidonic acid metabolism through lipoxigenase and scavenging of free radicals generated in this pathway; decreased expression of inflammatory cytokines IL- β , IL-6, and TNF- α ; and down regulation of protein kinase C (Jurenka, 2009).

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5.4 Gastrointestinal Effects

Curcuma longa also has several defensive effects on the gastrointestinal tract. Turmeric is generally used in spices for food and helps in inhibits the ulcer formation in gastric tract. It also helps in reduced the intestinal spasm and increase the bicarbonate, gastrin, and secretion of pancreatic enzymes. Study was performed on 25 patients with diagnosed gastric ulcer by endoscopy then 600 mg turmeric powder given five times daily. After five days therapy showed that 48 percent of patient were healed completely without adverse reactions (Khajehdehi *et al.*, 2012). Curcumin may also enhance the efficacy of current chemotherapeutics and, in combination with chemotherapy, may contribute an admirable strategy for treatment of gastrointestinal cancers (Patel *et al.*, 2009). The TRPV1 receptors are widely expressed in the entire gastrointestinal tract and enteric nervous system, and there is evidence that curcumin can inhibit GI nociception and reverse gut hypersensitivity by acting on peripheral terminals (Zhi *et al.*, 2013). Pharmacological properties of curcumin on TRPV1 could be a novel pain modulator (Barbara *et al.*, 2004).

5.5 Osteoarthritis

Osteoarthritis is a chronic inflammatory regressive process that affects joints such as the hips, hands, spine, knees. Some studies have shown that curcuma longa ingredients may effective in the treatment of degenerative disease or osteoarthritis. Generally, treatment of osteoarthritis is very tough by conventional treatment, restricted primarily to used nonsteroidal anti-inflammatory drugs, injections of corticosteroids and analgesics. This primarily therapy can lead to adverse effects such as gastrointestinal and cardiovascular problems, notably when used for long periods (Scarpignato *et al.*, 2015). Curcumin seems effective in the pathogenesis of osteoarthritis. The curcuminoids may exhibit an important role as anti-

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inflammatory, down-regulating enzymes as phospholipase A₂, cyclooxygenase-2, and lipoxygenases, and reducing TNF- α and interleukins-1 β (IL-1 β), IL-6, and IL-8. They also act as inducer of apoptosis in Fibroblast-like synoviocytes (FLS) (Akuri *et al.*, 2017). Curcumin could be a new paradigm and therapeutic opportunity for the treatment and management of osteoarthritis (Henrotin *et al.*, 2013).

6. AZADIRACHTA INDICA

The plant *Azadirachta indica*, known as neem, commonly found in India, Nepal, Bangladesh and Pakistan, has therapeutic application in several diseases like diabetes, cancer, hepatitis, malaria, smallpox and gout. It consists of many effective constituents including nimbidin, nimbolide and limonoids which helps in curing the diseases. Quercetin and β -sitosterol were first polyphenolic flavonoids purified from fresh leaves of neem and has shown antifungal, antitumor, and antibacterial properties (Govindchari *et al.*, 1998). In this particular section of our article, we have discussed the role of neem in the prevention and treatment of disease like inflammation, cancer and diabetes.

6.1 Anti-Inflammatory Activity

Neem has anti-inflammatory properties and studies reported on neem leaf extract showed significant and dose-dependent anti-inflammatory activity in carrageenan based acute inflammation and formaldehyde-induced sub-acute inflammation in rats (Koley *et al.*, 1994). In another study conducted by Naik *et al.*, 2014 neem seed oil (NSO) has shown beneficial effect in carrageenan-induced hind paw edema in albino rats. NSO showed 53.14% inhibition of edema at the dose 2mg/kg body weight after 4 hours of carrageenan injection (Naik *et al.*, 2014). *Azadirachta indica* leaf extract also reported protective against cigarette smoke (CS) and lipopolysaccharide (LPS) induced pulmonary inflammation in mice (Lee *et al.*, 2017).

6.2 Anti-Diabetic Activity

Role of neem root bark extract is very imperative against diabetes. An experiment conducted on the neem bark root extract (NRE) showed statistically significant result in 800 mg/kg dose (Patil *et al.*, 2013). Another study was performed to examine the pharmacological hypoglycemic action of *Azadirachta indica* in diabetic rats and the results revealed significant decrease in glucose levels when compared to control rats (Aker *et al.*, 2013). The compounds extracted from neem leaf has shown predicted binding property with diabetes mellitus type 2 protein enzyme target phosphoenol-pyruvate carboxykinase (PEPCK)

(Jalil *et al.*, 2013). Thus, *Azadirachta indica* have significant antidiabetic activity and could be a potential source for treatment of diabetes mellitus.

6.3 Anti-Cancer Activity

Reports from previous studies showed the potential of plant extract of neem on inhibition of growth of the malignant cells through apoptosis, tumor suppressor gene and few molecular cascades (Rahmani *et al.*, 2014). It consists of flavonoids and other ingredients which play a crucial role in inhibiting the progression of cancer within the system. Reports suggest that the high rate of flavonoid intake result in decreased risk of cancer (Marchand *et al.*, 2002). *Azadirachta indica* holds various constituents which activate tumor suppressor gene and inactivate the activity of several genes involved in the cancer progression such as NF-KB, VEGF and P13KAkt. It also activates cyclogenase pathway, apoptosis and NF-kB signaling. Another report showed ethanolic neem extract in accentuation of expression level of proapoptotic genes, like caspase-8 and caspase-3, and attenuation of expression level of Bcl-2 and mutant p53 in the 7,12dimethylbenz(a)anthracene-induced cancer cells (Subapriya *et al.*, 2006). A component of neem called as nimbolide is also responsible for the down regulation of cell survival proteins, including I-FLICE, cIAP-1, cIAP-2, Bcl-2, surviving and x-linked inhibitor of apoptosis protein, and upregulation of the proapoptotic protein p53 (Gupta *et al.*, 2011). Study conducted by Othman *et al.*, 2012 documented the effect of leaf extract on c-Myc oncogene expression in 4T1 breast cancer cells and BALB/c mice and showed significant suppression of c-Myc oncogene expression compared to the cancer control group (Othman *et al.*, 2012).

6.4 Anti-microbial Activity

Azadirachta indica ingredients are known to be effective on inhibition of microbes growth such as viruses, bacteria and pathogenic fungi. Some studies shows antimicrobial efficacy compared with standard irrigant sodium hypochlorite. Zone of growth inhibition of microbes suggest they had antimicrobial properties (Ghonmode et a., 2013). Also suggest that leaf extract of neem showed significantly greater zone of inhibition than sodium hypochlorite (3%) ((Ghonmodeet a., 2013). Neem leaves extract possess a wide range of antibacterial effect against gram positive and gram negative as well as against *Mycobacterium tuberculosis*(Chorpra et al., 1952). *In-vitro* studies shows growth inhibition of *Vibrio cholerae*, *Klebsiella pneumoniae*, and *M. pyogenes*(Satyavati et al., 1976). *Azadirachta indica* leaf extract also suggest *in vitro* antiviral activity against Vaccinia virus (Anushka et al., 2011),

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Chikungemya and measles virus, group B coxsackieviruses (Satyavati et al., 1999) and herpes simplex virus type-1 (Tiwari et al., 2010). *Azadirachta indica* leaves have quercetin and beta-sitosterol polyphenolic flavonoids which also shows antifungal activity (Govindachari et al., 1998). Neem aqueous extracts shows efficacy in the inhibition of spore germination against three sporulating fungi such as *C. lunata*, *H. pennisetti*, and *C. gloeosporioides* f. sp. *mangiferae* (Anjali et al., 2013).

Table 1: Representative table showing the effect of herbal medicines on different disease.

Botanical Name	Common Name	Medicinal Uses
<i>Withania somnifaria</i>	Ashwagandha, Winter Cherry, Withania	Anti-inflammatory Anti-diabetic Anti-cancer Anxiety and depression Cardiovascular protection Anti-thyroid activity
<i>Allium sativum</i>	Garlic, Garlic clove, Camphor of The poor	Anti-inflammatory Anti-diabetic Anti-cancer Antibacterial Antioxidant Cardiac arrest protection
<i>Curcuma longa</i>	Turmeric Haldi	Anti-inflammatory Anti-diabetic Gastrointestinal effects Osteoarthritis
<i>Azadirachta indica</i>	Neem	Anti-inflammatory Anti-diabetic Anti-cancer Anti-microbial Antifertility

6.5 Antifertility

Azadirachta indica oil have novel property for long term and reversible blocking of fertility (Riar et al., 1991). This is seems effective contraceptive of plant

origin, that is not associated with nontoxic side effects (Updhyay et al., 1991). The intra-vas administration of neem oil resulted in a block of spermatogenesis without affecting testosterone production. The *in-vitro* performed single intra-vas administered in to male rats which shows infertile as compare to control, that this strategy could be an alternate approach to vasectomy (Updhyay et al., 1993). Study are also performed by Gbotolorun *et al* to determine the effects of alcoholic extract of Neem flowers on the estrous cycle, ovulation, fertility and foetal morphology of cyclic in adult Sprague-Dawley rats. That shows estrous cycle of 80% of the rats was altered with a marked prolongation of the diestrus phase also significant reduction in the number of ova shed. Interestingly no anti-implantation / abortifacient nor teratogenic effect was observed in the rats treated with Neem flower (Gbotolorun *et al.*, 2008). Moreover, plant origin *Azadirachta indica* that contribute equally in non-invasive in administration, non-hormonal in action, non-toxic and that is relatively long-acting. That herbal medicine could be a better strategy for medicinal complications along with no major side effects.

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CONCLUSION

Prior to use of herbal plants as a part of traditional medicine it is very imperative to have a thorough understanding of its use in past and present. Herbal plant contains diverse constituents which have numerous pharmacological actions thus the key challenge relief on fact of obtaining standardized clinical data. Also, the data indicating the toxicity of herbal drugs is not up to date. The present review article reported anti-inflammatory, anti-diabetic, anti-cancer, anti-anxiety and depression, cardiovascular protection and anti-thyroid activity of herbal drugs shown in Table 1. Future research should be oriented towards exploration of the active component and elucidation of mechanism of action of herbal drug. Systematic standardized research is used by FDA regulation and standard clinical trials are quite limited and need to be actively pursued. Thus, it should be the prime duty of scientists and investigators to perform clinical surveys/trials adhering guidelines at the international level. This would definitely play an intricate role in development of herbal drugs as therapeutic components towards the wealth of mankind.

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