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CURRENT ADVANCES IN PHARMACOLOGICAL ACTIVITY AND TOXIC EFFETCS OF VARIOUS CAPSICUM SPECIES

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ABSTRACT: Nature always stands as a golden mark to exemplify the outstanding phenomena of symbiosis. Natural products from plant, animal and minerals have been the basis of the treatment of human disease. Capsicum plants belongs to the family Solanaceae and kingdom Plantae, consist of 27 species, and approximately 3000 varieties. Chili peppers are used worldwide in foods for their pungent flavor, aroma, and to prolong food spoilage. With capsaicin contents ranging from zero to millions of Scoville heat units, the different varieties offer a wide range of options for people all over the world. The aim of present review is to form a short compilation of the pharmacological and toxicological potentials of this multipurpose fruit. Capsicum, has been used as anti-inflammatory, anti-diabetic, anti-cancer, anti-ulcer, anticoagulant, analgesic, anti-arthritis, immuno-modulatory, memory enhancing, pain relief, hypocholesterolaemic, hypolipidemic, hepatoprotective and antimicrobial effects. It also cause irritation to mucous membrane, inflammation and neurotoxicity. It should not be used on open wounds or abrasions, or near the eyes. It has antagonistic effects on of α-adrenergic blockers, clonidine and methyldopa.

INTRODUCTION: Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. Wide range of pharmacological effects were recorded to different medicinal plants. The use of medicinal plants is a traditional form of providing relief from illness and can be traced back over five millennia in several civilizations. In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects [1-2].

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The search for new pharmacologically active agents obtained from plants has led to the discovery of many clinically useful drugs that play a major role in the treatment of human disease. According to the WHO in 2008, more than 80% of the world's population relies on traditional medicine for their primary healthcare needs [3].

Chili pepper is the most used spice in food throughout the world. From ancient times Capsicum plants are cultivated throughout the world [4]. Ninety percent of chilli is produced in Asia [5]. It comprises a diversified group of hot and sweet peppers originating in mainly tropical regions of the Americas and is widely cultivated in Asia, Africa, and Mediterranean countries; however, it is currently used by one fourth of the global population, owing to its versatility, including uses for chemical and pharmacological purposes.

The family contains about 90 genera and nearly 3000 species widespread in distribution. The genus consist approximately of 20-27 species, along with approximately 3000 varieties among the cultivated species *C. annuum* enjoys the highest morphometric diversity, and is cultivated almost all over the world [6-7].

2. Plant description:

2.1 Geographical source: Chillies are cultivated mainly in tropical and sub-tropical countries like India, Japan, Mexico, Turkey, United States of America and African countries. In Asia, India, China, Pakistan, Indonesia, Korea, Turkey and Sri Lanka; Nigeria, Ghana, Tunisia and Egypt in Africa; Mexico, United States of America in North and Central America; Yugoslavia, Spain, Romania, Bulgaria, Italy and Hungary in Europe and Argentina, Peru and Brazil in South America are the major chilling growing countries. India is the world leader in chilli production followed by China and Pakistan. The world area and production of chilli is around 1.8~2 million ha and 7 million tonnes respectively [5].

2.2 Vernacular names: Capsicum has various names in various languages. Some of them are shown in (**Table 1**) [8-9]

TABLE 1: COMMON NAMES OF CHILI

Afrikaan	Rissie
Arabic	Filfil-e-Ahmar
Austria	Paprika
Belgium	Peper
Bulgarian	Cherven Piper, Piperka
Chinese	Chiao-Tzu, Ching Chiao
English	Chillies, Long Chilies, Red Chillies
Farisi	Paprika
French	Piment Annuel, Gros Piment, Piment Doux
German	Cayennepfeffer, Chile, Chili, Chilli
Greek	Pipera, Piperia
Italian	Peperone, Pepperoncini, Pepperoncino
Japanese	Bansho, Bapurika, Peppaa
Malaysia	Cabai, Chili, Cili
Russian	Perets Krasnyj, Perets Zelenyi
Spanish	Aji, Chile, Chile Jalapento
Turkish	Biber

2.3 Taxonomy: Chilli belongs to the family Solanaceae and kingdom Plantae [10].

- Domain: Eukaryotes
- Kingdom: Plantae
- Phylum: Tracheophyta
- Subphylum: Euphyllophytina
- Class: Magnoliopsida
- Subclass: Lamiidae
- Superorder: Solananae
- Order: Solanales
- Family: Solanaceae
- Subfamily: Solanoideae
- Tribe: Solaneae
- Genus: Capsicum

2.4 Species of the Genus *Capsicum:* *Capsicum* species are small perennial herbs native to tropical South America. The majority of researchers believe that this genus is comprised of more than 20 species. The 5 most common ones believed to be a result of domestication are *C. annuum*, *C. baccatum*, *C. frutescens*, *C. chinense* and *C. pubescens* [11] (**Fig. 1**).

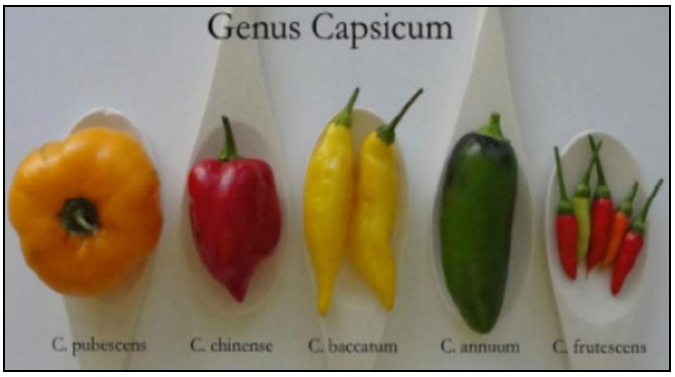

FIG. 1: VARIETIES OF CHILLI

The other species are exotic and not as widely distributed as these five. Below is a list of the other presently known species in (**Table 2**) [12].

TABLE 2: OTHER PRESENTLY KNOWN SPECIES

Capsicum buforum	*Capsicum lanceolatum*
Capsicum campylopodium	*Capsicum leptopodum*
Capsicum cardenasii	*Capsicum lycianthoides*
Capsicum ceratocalyx	*Capsicum minutiflorum*
Capsicum chacoense	*Capsicum mirabile*
Capsicum coccineum	*Capsicum mositicum*
Capsicum cornutum	*Capsicum parvifolium*
Capsicum dimorphum	*Capsicum pereirae*
Capsicum dusenii	*Capsicum ramosissimum*
Capsicum eximium	*Capsicum recurvatum*
Capsicum flexuosum	*Capsicum rhomboideum*
Capsicum friburgense	*Capsicum schottianum*
Capsicum galapagoense	*Capsicum scolnikianum*
Capsicum geminifolium	*Capsicum spina-alba*
Capsicum havanense	*Capsicum stramoniifolium*
Capsicum hookerianum	*Capsicum tovarii*
Capsicum hunzikerianum	*Capsicum villosum*

3. Constituents:

3.1 Chemical constituents: Peppers contain phenolics and flavonoids [13], carotenoids, Vitamin C, Vitamin E [14] and alkaloids [15] which play important roles in human health. The fruit of Capsicum contains capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) and several related chemicals containing a series of homologous branched and straight chain alkyl vanillylamides, collectively called capsaicinoids, as their chief chemical entity. The major capsaicinoids present are capsaicin (48.6%) is quantitatively followed by 6, 7-dihydrocapsaicin, minor capsaicinoids that are present are nordihydrocapsaicin (7.4%), homodihydrocapsaicin (2%), and homocapsaicin (2%). Other parts of the plant contain steroidal alkaloid glycosides (solanine, solanidine, solasodine).

The seeds contain the steroidal glycosides capsicoside A through D and all furostanol. Capsicum is rich in carotenoid pigments, including capsanthin, capsorubrin, carotene, luteine, zeaxanthin, and cucurbitaxanthin A. Other phytochemicals present are scopoletin, chlorogenic acid, alanine, amyrin, caffeic acid, camphor, carvone, cinnamic, citric acid, linalool, linoleic acid, oleic, piperine, Vitamin B_1, B_3, C, E and oleoresin [16].

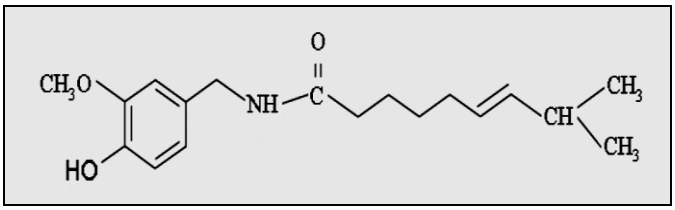

FIG. 2: STRUCTURE OF CAPSICUM

3.2 Nutritional Constituents: Capsicum is rich in Vitamin C (ascorbic acid) and Zinc. It is also high in Vitamins, A, C, rutin, beta carotene, iron, calcium and potassium. Capsicum also contains magnesium, phosphorus, sulphur, B-complex vitamins, sodium and selenium [17].

4. Pharmacological Potential:

4.1 Anti-inflammatory activity: Several authors have demonstrated that capsaicin has anti-inflammatory properties, such as the inhibition of the production of pro-inflammatory mediators as IL-6, TNF, PGE_2 and nitric oxide. It was found that the effect of capsaicin on the production of inflammatory molecules showed significant inhibition of production of LPS-induced PGE2 in a dose-dependent manner [18]. Phenolic and flavonoid compounds present in chilli have been reported as anti-inflammatory agents [19]. Capsaicinoids and capsinoids compounds have also been reported to exhibit anti-inflammatory activities [20].

The ethanolic and butanol extracts of *Capsicum baccatum* presented a significant anti-inflammatory activity toward carrageenan-induced pleurisy model in mice [21-22].

The anti-inflammatory activity of *Capsicum annuum* was assessed by inhibiting lipoxygenase (LOX) enzyme. The results showed higher % of LOX inhibition by green capsicum (46.12 %) followed by yellow (44.09 %) and red capsicum (32.18 %) [23]. Anti-inflammatory activity of *C. annum* was also reported by Monsereenusorn Y, (1980) [24].

4. 2 Anti-diabetic activity: The crude extract of fruit was found to inhibit intestinal glucose absorption which may be partially responsible for lowering blood sugar [24]. Regular consumption of chili may attenuate postprandial hyperinsulinemia [25]. Alpha glucosidase and α- amylase inhibitory activities of capsicum was evaluated by scientists [26]. Baek J. *et al*., (2013) investigated anti-diabetic activity of *Capsicum annuum* against α-amylase, α-glucosidase and angiotensin I-converting enzyme (ACE) inhibitors [27]. Gautami J. *et al*., (2015) also mentioned the anti-diabetic activity of chilli in their review articles [28]. Anthony OE *et al*., (2013) observed improvement in the biochemical parameters, blood glucose levels and body weight of alloxan induced diabetic Wistar rats [29].

4. 3 Anti-cancer activity: Anticancer activity of capsaicin was recorded in different types of cancer [20, 30]. Capsaicin has been reported to be effective, both *in vitro* and *in vivo* against the growth of prostate cancer cells inducing the apoptosis of both androgen receptor positive and negative prostate cancer cell lines associated with an increase of antibodies p53, p21, and Bax [31]. Capsaicin has an anti-cancer effect on human colorectal cancer and studied on HCT 116, LoVo, SW480, and Colo 205 cell lines.

It induced autophagy, induced anti-tumorigenesis, deregulation of B-catechin, and TCF dependent signaling [32-33]. Anti-cancer activity of capsaicin on human breast cancer was studied on MCF-7, T47D, BT-474, SKBR-3 and MDA-MB231 cell lines where it causes mitochondrial dysfunction [34], increased apoptosis and arrest cell cycle into G2/M phase [35-38]. Human myeloid leukemia also recovered by capsicum and studied on HL-60, U937 and THP-1 cell lines where it enhances the apoptotic effects by activating the calcium-CaMKII-Sp1 pathway [38].

Human esophageal epidermoid carcinoma also cured by capsaicin worked on CE 81T/VGH cell lines and found that it induced apoptosis and G0/G1 phase cell cycle arrest [37]. Capsaicin inhibited cell growth and promoted apoptosis on A375 cell line on human melanoma [37, 39]. Anti-cancer activity of capsaicin against pancreatic cancer has successfully evaluated on PANC-1 cell line where it induced G0/G1 phase cell cycle arrest and apoptosis and ultimately arrest tumour growth [32, 40-41]. Capsicum inhibit human hepatoma on HepG2 cell line by decreasing cell viability, generated ROS, activated caspase-3, induced apoptosis and autophagy [42]. It also enhances apoptotic effects by activating the calcium-CaMKII-Sp1 pathway on Hep3B cell lines [38]. Human nasopharyngeal carcinoma was recovered by capsicum studied on NPC-TW 039 cell lines by inducing G0/G1 phase arrest, apoptosis and increased cytosolic Ca2+ level [43]. Lin CH *et al.*, (2013) found that treatment of KB cells with capsaicin significantly reduced cell proliferation/ viability and induced cell death in a dose-dependent manner. Cell cycle analysis indicated that exposure of KB cells to capsaicin resulted in cell cycle arrest at G2/M phase [43]. Capsicum was also reported to be effective against gastric cancer by inducing apoptosis and modulates MAPK signaling [44-45].

4. 4 Anti-ulcer activity: Chilli, as well as capsaicin, has a protective effect on ethanol- or aspirin-induced lesion formation in the rat gastric mucosa. Long-term chilli intake (360 mg daily for 4 weeks) protects against haemorrhagic shock-induced gastric mucosal injury in the rat, an effect which may be mediated by capsaicin-sensitive afferent neurons [46]. Capsaicin prevents gastric mucosal microbleeding and can be successfully used for the eradication of *Helicobacter pylori* induced mucosal damage [47].

The effect of aqueous extracts of *Capsicum frutescens* on the healing acute gastric ulcer was investigated in rats at doses of 300 and 600 mg/kg body weight for seven days. The results revealed that oral administration of the aqueous extract at a dose of 600mg/kg body weight, reduced the length of gastric ulcer, volume of gastric juice, and improved histopathological changes [48]. Capsaicin pretreatment reduces the gastric acid secretion elicited by histamine. Mozsik G *et al*., (1999) shows that, small doses of capsaicin given intragastrically inhibit gastric basal acid secretion in healthy human subjects [49].

4. 5 Anticoagulant activity: The use of capsaicin at therapeutic doses (2.5-10.0 mg/kg) may reduce thromboembolism without any clinically relevant alteration in platelets [50]. Capsaicin inhibited platelet aggregation and the activity of clotting factors VIII and IX, a property which reduce the incidence of cardiovascular diseases. It has been suggested that capsaicin was able to pass through plasma membrane of platelets and alter membrane fluidity [51]. Recent studies showed that due to presence of TRPV1 in human platelets, capsaicin induces Ca^{2+} release from intracellular platelet stores and subsequently contributed to ADP and thrombin induced platelet activation [52]. *Capsicum frutescens* extract showed synergistic activity with streptokinase on thrombolysis [53]. Anti-coagulant activity of capsicum was also reported by other scientists [54-56].

4. 6 Analgesic activity: Both capsaicin and *Capsicum frutescens* Linn. (Solanaceae) fruit aqueous extract have dose dependent, statistically significant peripheral and central analgesic properties on mechano-thermal and chemically-induced pain [57]. Capsaicin extracted from *Capsicum spp* act at the vanilloid receptors and has proved very useful in intractable pain of diabetic neuropathy, as well as herpetic and trigeminal neuralgia [58]. Most of the studies have shown the analgesic effect of capsaicin in spinal mechanism. The protection of pre-treated rats from thermal pain was described by Ojewole JA, (2002) [59].

Carotenoids extracted from dried *Capsicum annuum* were also evaluated for their analgesic activities. Carotenoids extracts exhibited significant peripheral analgesic activity at 5, 20, and 80 mg/kg and induced central analgesia at 80 mg/kg [60].

4. 7 Anti-arthritis activity: Ethanolic extracts of *C. annum* effectively controlled arthritis development. The arthritis scores of AIA (adjuvant induced arthritis) were significantly decreased in hot pepper leaf of (*C. annum*) treated mice, as indicated by reduction in ESR, CRP and cytokine levels [61]. A nanovesicle topical formulation prepared with the semipurified capsaicinoids extract demonstrated good anti-arthritic activity in rat model, in the reduction of joint swelling and pain. The nanovesicle formulation showed better tolerability and acceptance on both animal and human models [62]. Paste of leaves are applied locally for the treatment of arthritis [63].

4.8 Immuno-modulatory effect: The immunological effects of red pepper (*Capsicum annuum* L.) extracts and its main pungent capsaicin was investigated on T helper 1 (Th1) and 2 (Th2) cytokine production in cultured murine Peyer's patch (PP) cells *in vitro* and *ex vivo*. Direct administration of capsicum extract (1 and 10 mug/ml) and capsaicin (3 and 30 muM) resulted in suppression of interferon (IFN)-gamma, interleukin (IL)-2, IL-4 and IL-5 production. In an *ex vivo* experiment using PP cells removed from the mice after oral administration of capsicum extract (10 mg/kg/day) for 4 consecutive days, IL-2, IFN-gamma and IL-5 increased in response to concanavalin A (Con A). Oral administration of 3 mg/kg/day capsaicin, also enhanced IL-2, INF-gamma and IL-4 production in response to Con A stimulation but did not influence the production of IL-5 [64]. It appeared that dendritic cells, a key cell type in immune responses, have the receptor for capsaicin, and engagement of this receptor has powerful immune consequences.

In addition, the administration of CAE attenuated ovalbumin-induced increases in NF-κB activity in lungs [65]. Capsicum extract and capsaicin modulate T cell-immune responses, and their immunomodulatory effects on are partly due to both TRPV1 dependent and independent pathway [66].

4.9 Memory inhancing activity: Green chilli is a promising memory enhancer. The underlying mechanism of action of green chilli appears to be dependent on- i) improvement of memory in exteroceptive models ii) reversal of memory deficits iii) enhanced scavenging of free radicals and iv) inhibition of AChE enzyme. There was a significant rise in the levels of glutathione levels in the brains [67]. Suganma H *et al*., (2004) shows that 0.1% (w/w) capsanthin displayed a considerable improved memory acquisition [68].

4.10 Pain relief: Capsaicin administered topically, intradermally, or orally has proven to a reliable and reproducible way to investigate peripheral and central mechanisms underlying certain hypersensitivities and to be a useful treatment of certain pain states, including neuropathies [69]. With neuropathic pain in mind, animal studies using intrathecal as well as subcutaneous or topical capsaicin have produced significant improvements in the relief of hyperalgesia and pain [70]. Pain relief activity of capsicum was also reported by other scientists [58-59].

4. 11 Hypocholesterolaemic and hypolipidemic activity: The plasma total cholesterol, triglyceride, LDL-C, VLDL-C, and VLDL-TG levels and the atherogenic index were all decreased, whereas the HDL-C level was higher in rabbits fed with 1% red pepper. Supplementation of red pepper increased fecal triglyceride excretion and showed fewer fat droplet deposits in the aorta [71]. Capsicum oleoresin (75 mg/kg bw/day) showed reducing effect in serum cholesterol and triglycerides levels in hypercholesterolemic gerbils. The red pepper or its active principle capsaicin showed significant reduction in rise of liver cholesterol and brought enhanced faecal excretion of both free cholesterol and bile acids in female albino rats. The hypocholesterolemic action of capsaicin is likely to be responsible for the presence of common vanillyl moiety [72].

4. 12 Respiratory agents: Cough reflex sensitivity to capsaicin is used as a testing mechanism in human pharmacological and clinical research [73]. In human, capsaicin desensitized nasal mucosa and reduced allergic symptoms of nasal allergy or pain induced by other agents.

Respiratory effects of capsicum involve cough reflex stimulation via capsaicin-sensitive nerves and bronchoconstriction. Capsicum can cause laryngeal and pulmonary oedema and chemical pneumonitis but this is rare [74].

4. 13 Effect on cornea and conjunctiva: Oleoresins isolated from capsicum in the form of spray causes eye pain, stinging or burning, increase of tear secretion, temporary blindness, rarely, corneal abrasion, mouth and nose burning, runny nose, sneezing, choking sensation, breathing difficulties and asthma in patients with bronchoconstriction. Its local effects include rash, dermatitis, eczema and erythema on the affected area of skin, vesicles and blisters in a long-term exposure, headaches, dizziness, vomiting, pulmonary edema, acute respiratory failure, hypotension, chest pain and motor control loss. Oleoresin capsicum spray can affect both morphology and sensitivity of the cornea [74-75]. Capsicum decrease aqueous humor production [76].

4. 14 Hepatoprotective activity: Capsaicin has shown hepatoprotective activity against carbon tetrachloride (CCl_4) induced liver injury in rats. Capsaicin produces a protective effect in rat lung and liver by strengthening the pulmonary antioxidant enzyme defense system [77].

4. 15 Anthelminthic activity: The anthelmintic activity of methanolic extract of fruits of *Capsicum frutescens* L. were carried out by Kamal ATMM *et al.,* (2015). The anthelmintic activity was determine at two different stage 'time of paralysis' and 'time of death' of the worms. Time for paralysis was noted when no movement of any sort could be observed except when the worms were shaken vigorously. Death was concluded when the worms lost their motility followed with fading away of their body colors. In case of *C. frutescens* the mean paralyzing time of *Tubifex tubifex* with the dose of 2.5, 5 and 10 mg/ml were found to be 18, 5 and 3.43 minutes respectively and the mean death time of *Tubifex tubifex* with the dose of 2.5, 5 and 10 mg/ml were found to be 37.92, 21.04 and 5.89 minutes respectively for *C. frutescens* [78].

4. 16 Antibacterial effects: Chilli has been reported to exhibit significant antimicrobial activity against many microorganisms such as *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* [79]. Methanolic extract of red pepper was tested and found to be effective against multi-drug resistant *Vibrio cholerae* [80]. Antimicrobial peptides isolated from chilli has been found effective against a few types of yeast such as *Candida cerevisiae*, *Kluyveromyces marxiannus*, *Pichia membranifaciens*, *Saccharomyces cerevisiae*, *Candida tropicalis*, *Candida parapsilosis* and *Candida albicans* [81].

Kalia NP, (2012) evaluated the possibility of capsaicin acting as an inhibitor of the NorA efflux pump of *S. aureus*. The minimum inhibitory concentration (MIC) of ciprofloxacin was reduced 2 to 4 fold in the presence of capsaicin [82]. In a different study, Chatterjee *et al.,* (2010) determined that the methanol extract of red chili, and purified capsaicin could inhibit cholera toxin (CT) production in recently emerged *V. cholera* [83]. In another experiment it is determined that capsaicin inhibited growth of *H. pylori* in a dose-dependent manner at concentrations above 10 μg/ml [84].

The ethanol extract (100 mg/ml) of *Capsicum annuum* showed high antimicrobial activity against *Micrococcus sp* (20 mm), *Bacillus* (10 mm), *E. Coli* (17 mm), *Pseudomonas sp* (16mm) and *Citrobacter sp* (15 mm). The chloroform extract of *Capsicum annuum* showed less antimicrobial activity against all the tested pathogens [85]. The inhibitory effect of the extract of *Capsicum annuum* bell pepper type was also evaluated against *Salmonella typhimurium* and *Pseudomonas aeruginosa*, and found that against *P. aeruginosa*, it shows bacteriostatic effect, while against *Salmonella typhimurium* its shows bactericidal effect [86].

Antibacterial activity of *Capsicum annuum* was also evaluated against pathogenic bacteria isolated from the urinary tract (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *E. coli*) here the concentration lies between 5-10mg/ml [87]. Kwamboka NJ *et al.,* (2016) evaluated antibacterial activity of *Capsicum frutescens* extracts against *Pectobacterium carotovorum* [88]. Sandhya MVS *et al.,* (2016) conducted comparative study on eight species of Capsicum and its vertices such as *Capsicum annuum*. var. *Capsicum chinense*,

Capsicum annuum var. and others against two human pathogens *Staphylococcus aureus* and *Streptococcus mutant* [89]. Anti-bacterial activity of capsicum was also evaluated by other scientists [90-100].

4. 17 Anti-fungal activity: CAY-1, a novel saponin isolated from *C. frutescens*, was found to be active against 16 different fungal strains, it acted by disrupting the membrane integrity of fungal cells [101]. The antifungal potential of aqueous leaf and fruit extracts of *Capsicum frutescens* against many fungus (*Aspergillus flavus, A. niger, Penicillium* sp. and *Rhizopus* sp) was studied. The minimum inhibitory concentrations (MIC) and minimum fungicidal concentration (MFC) of *C. frutescens* extracts were determined. MIC values of the fruit extract were lower compared to the leaf extract [102]. The literature review demonstrates that extracts and isolated peptides from chilli have been reported for their effectiveness against various microbes including, fungi [103]. Pereeira JAP *et al.,* (2016) evaluated anti-fungal activity of *Capsicum annuum* against *Arbuscular mycorrhizal* [104]. Latef AHA (2011) also determined anti-fungal activity of *Capsicum annuum* [105].

4. 18 Antiviral activity: Capsicum has been found to be rich in chemicals that are potent against a range of viruses, an example is cis-capsaicin, which is active against herpes simplex virus (HSV) ailment in guinea pigs. Cis-capsaicin is reported to block viral replication cycle. Similarly, capsaicin has been reported to exhibit special effects on sensory neurons, which are directly involved in spreading and persistence of HSV infection [106]. Antiviral activity of capsicum also evaluated by Pereeira JAP *et al.,* (2016) [104].

4. 19 Cardiovascular effects: Many studies showed that capsaicinoids had beneficial effects on the cardiovascular system to treat ischemic heart disease, hypertension and atherosclerosis [107]. In anesthetized dogs intravenous injections of capsaicin (10-300 μg/kg) caused a transient rise in mean systemic blood pressure followed by a sustained fall, whereas in anesthetized rabbit's capsaicin caused only hypotension [108]. Capsaicin, when fed along with cholesterol-containing diets to female albino rats, it prevented significantly the rise of liver cholesterol levels [109].

4. 20 Pruritus: Capsaicin largely contributed to the gradual healing of the skin lesions. Topical capsaicin has been shown to effectively treat pruritus associated with psoriasis. It is found that, 24 h of treatment with capsaicin caused a 15% decrease in perfusion in lesional skin and pityriasis rubra pilaris (PRP) which is characterized by redness of the skin, scaling and a variable degree of pruritus [110]. It is found that a patient with extremely itchy PRP treated with capsaicin was apparent relieved [111]. Capsaicin is also used in the treatment of prurigo nodularis, which is an eruption of lichenified or excoriated nodules caused by intractable pruritus and pruritus ani (intense itching localised in the anus and perianal Skin) [112].

4. 21 Rhinitis: A study conducted by Snider M. (1992) found that rhinitis, sneezing, and congestion were alleviated in patients who received repeated nasal sprays of capsaicin [113]. In a placebo-controlled study, intranasal capsaicin was shown to be effective in reducing nasal symptomatology in nonallergic, noninfectious perennial rhinitis without affecting cellular homeostasis up to 9 months after treatment [114]. Fokkens W *et al.*, (2016) mentioned the activity of capsicum against rhinitis but it is not effective for elderly patient on rhinitis [115]. Other scientist are also determined activeness of capsicum against rhinitis [116-117].

4. 22 Anti-obesity effect: Capsaicin present as one of the chemical constituents has been proved to have anti-obesity activity. Dietary capsaicin enhances the expression of adiponectin and its receptor thereby reducing metabolic dysregulation in obese diabetic mice. The effects of capsaicin in liver and adipose tissue are due to its dual action on peroxisome proliferator-activated receptor alpha and transient receptor potential vanilloid-1 expression/activation. Upon capsaicin treatment in white adipose tissue thermogenesis and lipid metabolism-related proteins are altered. Capsaicin inhibits adipogenesis in preadipocytes and adipocytes and induces apoptosis. Ingestion of capsaicin is associated with increase in energy expenditure through the activation of brown adipose tissue thereby increasing fats oxidation and improving lipolysis [118]. The anti-obesity effects of water extracts of *Capsicum annuum* L. varieties, were examined through the evaluation of

lipoprotein lipase (LPL) mRNA expression level in 3T3-L1 cells (mouse pre-adipocytes) [119].

4. 23 Weight management: Capsaicin was found to reduce body fat accumulation in animal experiments as well as clinical studies. The anti-obesity effect of capsaicin showed that thermogenesis and lipid metabolism related proteins were markedly altered upon capsaicin treatment. Studies reveal that body temperature and oxygen consumption increase with regular intake of it and can promote reduction of body weight and oxidation of body fat [120]. Increasing a person's energy expenditure and reducing their appetite could be of great assistance in helping and maintaining weight loss [121].

4. 24 Cough challenge: Capsaicin, the pungent extract of red peppers, has achieved widespread use in clinical research because it induces cough in a dose-dependent and reproducible manner [122]. *Capsicum annuum* (red pepper) is a fruit spice of the Solanaceae family, rich in proteins, lipids, vitamins, carbohydrates, and health phytochemicals such as carotenoids, flavonoids and capsaicinoids known to prevent diseases such as asthma, coughs, sore throats etc. Other scientist are also reported similar activity of capsicum [123-124].

4. 25 Dermatological conditions: The topically applied capsaicin, a known inhibitor of cutaneous vasodilatation produces relief on moderate and severe psoriasis. Significantly improved reduction in scaling and erythema was observed. Burning, stinging, itching, and redness of the skin were noted by nearly half of the patients on initial applications of study medication but diminished or vanished upon continued application which suggest that topical application of capsaicin may be a useful in the treatment of psoriasis [125]. Capsaicin was successfully used in treatment of acute lipodermatosclerosis and acute lobular panniculitis in pregnant woman [126].

5. Adverse effects and toxicity:

5.1 Dermatological injury: Initial contact of capsaicin with skin or mucous membranes produces a violent irritation with subsequent desensitization. Victims experience acute burning pain, tingling, erythema, edema, and pruritus. In prolonged exposure and in severe cases, persistent dermatitis with severe erythema and/or blister formation may occur [127].

5.2 Ophthalmic injury: Contact of the eye with capsicum causes redness, swelling, lacrimation, and involuntary or reflex closing of the eyelids. More severe symptoms include persistent pain, foreign body sensation, photophobia, discharge or exudate, or peri-orbital oedema [128]. Decreased tear production, impaired corneal reflex lacrimation and corneal blink reflex have also been observed [129]. The toxic effects of capsicum on eye was also reported by many other scientists [127,130-134].

5.3 Nasal and respiratory toxicity: Exposure may occur through inhalation, causing immediate inflammation of mucous membranes. Throat irritation results in a burning sensation, cough, choking, and inability to speak (due to laryngospasm or laryngeal paralysis). In the nasal mucosa, capsicum produces irritation, burning pain, sneezing, and a dose-dependent serous discharge [135]. Other respiratory symptoms have also been reported, including severe coughing, mucus secretion, shortness of breath, bronchoconstriction presenting as wheeze, and chest tightness [136]. Inhalational exposure to capsaicinoids in pepper sprays damaged rat bronchial, tracheal, nasal, alveolar cells and causing acute inflammations [137].

5.4 Gastrointestinal problem: Internally, Capsicum may cause gastrointestinal cramping, pain, and diarrhoea. Topically, it may cause painful irritation of mucous membrane. High doses administered capsaicin over extended period of time can cause chronic gastritis, kidney damage, liver damage and neurotoxic effects [138].

5.5 Systemic toxicity: Some studies have reported systemic symptoms including disorientation, fear, loss of body motor control (*e.g*. diminished hand-eye coordination), hyperventilation, tachycardia, and pulmonary oedema. The acute increase in blood pressure could cause headache, increased stroke risk and heart attack [136].

5.6 Drug Interaction: Interactions were reported with concomitant administration of *Capsicum annuum* with aspirin and salicylic compounds. It also decreased the actions of α-adrenergic blockers, clonidine and methyldopa [132].

CONCLUSION: Most research focused on the identification and characterization of active principles from crude extracts of medicinal plants. However, many hidden therapeutic molecules are present in the crude plant drugs all of them should be brought into lime light. In this review article, an attempt has been made to aggregate the reported pharmacological potential of chilli in consideration to the health aspects. The chilli is used as promising medicinal plants with wide pharmacological activities which could be utilized in several medical applications as a result of their effectiveness and safety.

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