




# Expatriating the Therapeutic Profile of Garlic (*Allium sativum*): a Bench to Bedside Approach

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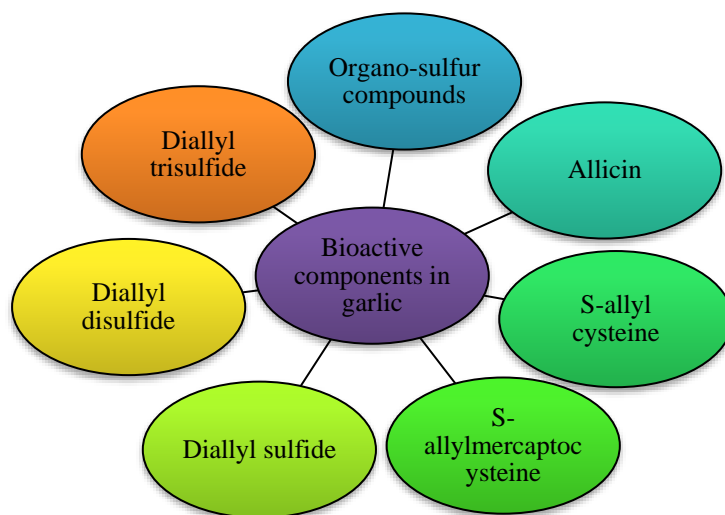
**Abstract:** Garlic (*Allium sativum*) is amongst the oldest medicinal plant in centuries. It is an amazing plant that contains numerous bioactive components such as organosulfur compounds, allicin, s-allyl cysteine, S-allyl-mercapto cysteine, diallyl sulfide, diallyl disulfide, and diallyl trisulfide. This review discusses numerous valuable effects and therapeutic potential of garlic in treating several diseases such as cancer, obesity, diabetes, liver injury, hypertension, inflammation, viral infection, and arthritis. The enormous immunomodulatory, anti-oxidant, and anti-microbial characteristics of garlic have also been explained briefly. This review article also gives insight into the nanotechnology-based phytopharmaceuticals of garlic; has summarized pre-clinical models, clinical trials, and patents published about garlic's therapeutic applications and its phytoconstituents in the management of several disease conditions. This review article brings more attention to garlic, providing effective scientific proof for improved utilization of garlic in human health and disease control.

**Keywords:** *Allium sativum*; allicin; garlic; diallyl sulfide; diallyl disulfide; diallyl trisulfide; organosulfur; s-allyl-mercapto cysteine.

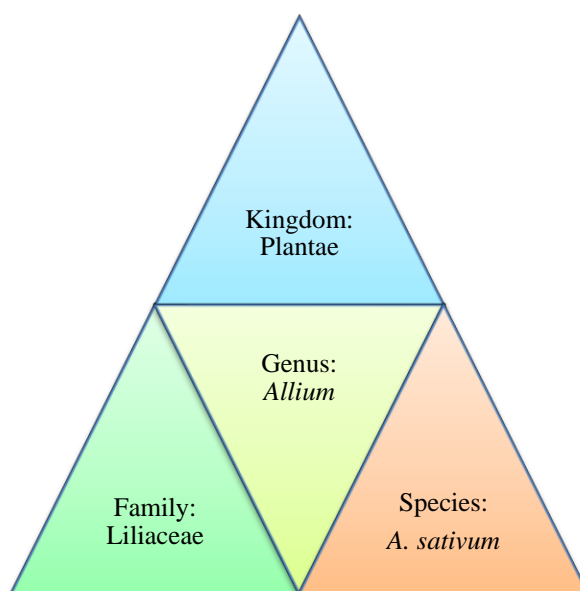
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## 1. Introduction

Garlic (*Allium sativum*) is the oldest therapeutic plant. It is a wonderful plant that has various bioactive compounds like organosulfur compounds (OSCs), allicin, s-allyl cysteine (SAC), S-allyl-mercapto cysteine (SAMC), diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) [1] (Figure 1). Taxonomic details of garlic have been represented in Figure 2. This review discusses various important effects and therapeutic potential of garlic in managing several diseases such as cancer, obesity, diabetes, liver injury, hypertension, inflammation, viral infection, and arthritis. The excellent immunomodulatory, anti-oxidant, and anti-microbial characteristics of garlic have also been described in brief. Traditional phytomedicines of garlic have certain drawbacks like poor aqueous solubility and lesser lipophilicity, causing diminished absorption and bioavailability. However, the application of nanotechnology in the development of nano-based phytopharmaceuticals overcomes these disadvantages. This review article also gives perspective into the nanotechnology-based therapeutics of garlic; has compiled pre-clinical prototypes, clinical trials, and patents reported about the medical strategies of garlic as well as its phytoconstituents in mitigation of many illnesses [2].



**Figure 1.** Bioactive compounds in garlic.



**Figure 2.** Taxonomic classification of garlic.

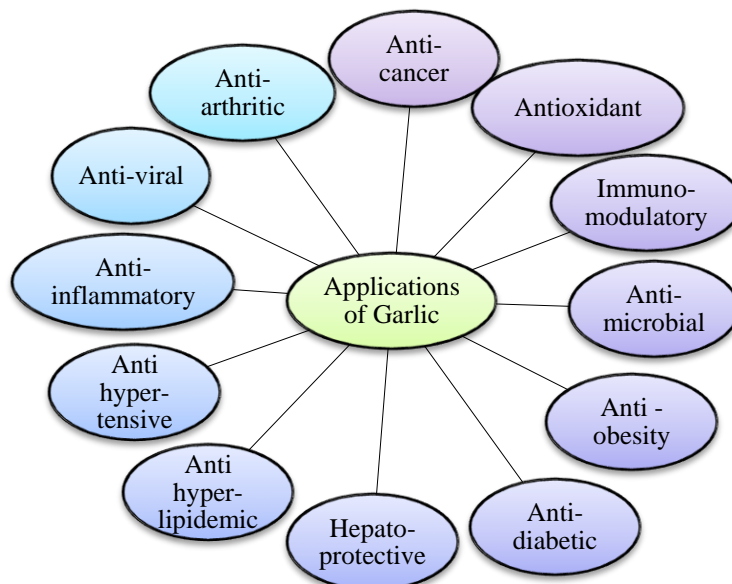
## 2. Therapeutic Applications of Garlic

Throughout previous years, garlic has been used to counter several illnesses, as depicted in Figure 3 [2,3].

### 2.1. Applications of garlic in cancer therapy.

Garlic and its constituents are successful in preventing and controlling various cancers [5,6]. This research has focused that garlic has been used as a medicinal agent for thousands of years. This has been successfully investigated that SAC and SAMC and some OSCs obtained from aged garlic leaf extract had the highest radical scavenging activity and reported to pervert the expansion of chemically induced as well as transplantable malignancies throughout many laboratory animals that infer that garlic can provide a type of melanoma prevention [7]. A group of researchers documented considerable applications over the use of OSCs isolated from garlic in cancer treatment mitigation as well as chemotherapy [8]. In another study, the activity of allicin in triple-negative breast cancer was discovered [9]. Various chemical compounds found

in garlic, specifically thioallyl constituents attributed to its anti-carcinogenic properties, and have been shown to impede the covalent binding of toxins to genetic material. They also accelerate cytotoxicity deterioration, have anti-oxidant and radical scavenging characteristics, and control cell proliferation, apoptosis, and immune cells. These have created a new pathway for studies in the area of chemotherapeutic agents and will further investigate the function of garlic in the treatment of health disease [10].



**Figure 3.** Versatile applications of garlic in several illnesses.

### 2.2. *Garlic as an excellent anti-oxidant.*

Anti-oxidants play a critical role in establishing balanced free radicals in the body. Superoxide is among the cell's principal free radicals, which changed massively under stressful circumstances [11-13]. Another group of researchers reported that aged garlic extract (AGE) isolated across the longer duration of 20 months is affluent in anti-oxidants, *i.e.*, OSCs, which destroyed free radicals and inhibited oxidative damage [14]. A group of researchers investigated that AGE contains SAC, SAMC, and OSCs with strong anti-oxidative activity [15]. Other groups of researchers investigated the anti-oxidant action of garlic and its phytoconstituents [16-19].

### 2.3. *Immunomodulatory activity of garlic.*

Garlic displays different bioactive molecules that boost immune function. Polysaccharides and their selenylated form procured from fresh garlic demonstrate a more intense immunomodulation function in contrast to black garlic [20,21]. This was investigated that garlic's IM characteristics are attributed to OSC (allicin), lectins, agglutinins, water-soluble fructans, fructosyl-arginine, SAC, and SAMC [20]. AGE has superior immunomodulatory (IM) properties than fresh garlic, and the effects are being ascribed to the regenerated OSCs [22,23]. Alkreathy and his researcher explored that AGE-treated mice survived for a longer time in contrast to control animals. An improved immune reaction in BALB/c mice with fibrosarcoma cancer has been reported with AGE [24]. Another group of researchers examined that AGE considerably lowered antigen-specific ear inflammation. The research implies that AGE might be a suitable choice as an immune modifier in IgE-mediated allergic mouse design [25].

#### 2.4. *Anti-microbial potential of garlic.*

Garlic has a broad spectrum of anti-microbial potential, and garlic oil impeded the *Penicillium funiculosum* fungus, probably invading and damaging the cellular structure [26,27]. Besides, raw garlic therapy reduced *Helicobacter pylori* in the patient's stomach in a clinical trial [28]. Anti-microbial activity of purple and white garlic extracts against oral microbial found that MIC against nine streptococci strains for white and purple garlic was 0.5-32.0 and 8-64 mg/ml, respectively. It was found that garlic's 2.5% solution as a mouthwash has bactericidal activity in five-week research in 30 subjects [29]. It has been investigated that ethanolic isolates from fresh garlic have anti-microbial activities against several microorganisms except lactic acid bacteria and yeast [30]. Other groups of researchers investigated the effect of garlic on the oral microbiome [31], explored garlic as an antidote [32], and studied the anti-biofilm effect of nanoparticles loaded with garlic extract [33].

#### 2.5. *Garlic in obesity and hyperlipidemia.*

Obesity is viewed as a serious public health problem [34]. A group of researchers investigated the anti-obesity action of lactic acid fermented garlic extract (LAFGE) in C57BL/6J mice and discovered that it works through adipose tissue hypertrophy inhibition via restraining adipogenesis [35]. Other groups of researchers investigated the anti-obesity effect of garlic's bio-actives [36], garlic oil [37], black garlic's melanoidins [38], potentiating action of diallyl disulfide on the anti-obesity activity of green tea [39], and activity of garlic supplement on pro-inflammatory factors in obesity [40]. It has been investigated the anti-obesity effects of garlic oil in the Sprague-Dawley rat model of high-fat diet-induced obesity and discovered that it could be due to enhanced UCP1 expression [41]. Researchers investigated the antihyperlipidemic and anti-obesity efficacy of garlic in obese patients with diabetes mellitus [42] and garlic oil in high-fat diet-induced hyperlipidemic rats [43].

#### 2.6. *Garlic in management of diabetes mellitus.*

Garlic and bioactive components can be protective against diabetes mellitus. Garlic has a longstanding experience as a natural remedy. The anti-oxidant, anti-inflammatory, and antiglycative activities of garlic are accountable for garlic's involvement in reducing the development of diabetes and the occurrence of diabetes-related complications [44-46]. Researchers explored the beneficial effect of garlic extract in diabetes mellitus through DPP-4 inhibition [47]. Another group of researchers explored that garlic oil nanoemulsion could alleviate diabetes mellitus induced nephropathy [48]. In another study, garlic extract's hypoglycaemic characteristics for mitigation of complications in streptozocin/nicotinamide-induced diabetic rats were investigated [49].

#### 2.7. *Hepatoprotective action of garlic.*

A group of researchers found that novel LAFGE based functional-food (D-18-007) has superior choleric and hepatoprotective action in acute liver injury [50]. Another group of researchers investigated that single-clove garlic has superior hepatoprotective activity compared to multi-clove garlic in carbon tetrachloride (CCl<sub>4</sub>)-induced liver injury [51]. In another research, the hepatoprotective effect of fermented black garlic extract in CCl<sub>4</sub>-induced acute hepatic injury in mice was examined [52].

### 2.8. *Garlic in management of hypertension.*

A group of researchers examined the blood pressure-lowering activity of garlic in a two-kidney-one-clip (2K1C) hypertensive rat model and identified a negative correlation between garlic intake and blood pressure [53]. A group of researchers investigated that raw garlic extract could be used to treat hypertension, as investigated in 2K1C rats [54]. Another group of researchers investigated the anti-hypertension efficacy of garlic [55-57].

### 2.9. *Garlic as an anti-inflammatory.*

Garlic has an anti-inflammatory action, which could be credited to its high OSC content [36,58]. A group of researchers examined the anti-inflammatory effect of garlic extracts. Through an enzyme-linked immunosorbent assay, it was found that cytokine and chemokine levels were significantly diminished in bronchoalveolar fluid [59]. Another research has investigated that aged garlic extract contains three sulfur amino acids like *S*-allyl cysteine, *S*-1-propenyl cysteine, and *S*-allyl-mercapto cysteine, which exhibited synergistic activity in mitigating inflammation in human gingival epithelial cells [60].

### 2.10. *Antiviral activity of garlic.*

Another group of researchers studied the antiviral activity of garlic extract against influenza virus in Madin-Darby Canin Kidney (cell culture and explored inhibitory effect extract on virus penetration and proliferation [61]. The potential antiviral effect of Garlic oil was investigated against Newcastle disease through incubation of LaSota viral strain along with garlic oil for 1 and 24 hrs and detected viral surface proteins and genome [62].

### 2.11. *Anti-arthritis activity of garlic.*

A group of researchers investigated that diallyl trisulfide extracted from garlic bulb produced potential anti-arthritis activity in a mouse model of collagen-induced arthritis [63]. Another group of researchers evaluated the potential anti-arthritis activity of DADS (20 and 50 mg/kg) in complete Freund's adjuvant-induced arthritic rat model [64].

## 3. **Limitations of traditional phyto-medicines of garlic**

Traditional phyto-medicines of garlic demonstrate superior in-vitro therapeutic activity and diminished side effects but show lesser *in-vivo* efficacy due to poor aqueous solubility, lipophilicity, and improper molecular size in poor absorption and lesser bioavailability [65].

## 4. **Application of nanotechnology-based phytopharmaceuticals of garlic**

Phyto-pharmaceuticals are natural remedies whose potency is due to one or more active ingredients or plant substances. Since prehistoric times, phytopharmaceuticals are often used for various illnesses. The development of a nano-based formulation of phyto-components provides several benefits such as solubility and bioavailability enhancement defend from toxicity, improvement of pharmacological action, upgrading of stability, and safeguard from chemical/physical degradation [65]. Therefore, garlic phytoconstituents have been incorporated into nanotechnology-based phytopharmaceuticals. Table 1 summarizes various types of recent nano-formulations of garlic, excipients involved, and their outcomes.

**Table 1.** Applications of nanotechnology in the production of phytopharmaceuticals of garlic.

| Phytoconstituents [Nano-formulation]         | Excipients   | Outcome   | Ref. |
|--|--|---|------|
| Diallyl disulfide [Niosomes]                 | Cholesterol, Span 20, Span 40, Span 80, Dicetyl phosphate  | Superior treatment of murine candidiasis  | [66] |
| Diallyl disulfide [Solid lipid nanoparticle] | Palmitic acid, Poloxamer 188   | Enhanced anticancer effect through induction of apoptosis                           | [67] |
| Diallyl disulfide [Solid lipid nanoparticle] | Palmitic acid, Poloxamer 188, Sodium dodecyl sulfate, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride   | Promising approach for improving anti-tumor activity and reduced off-target effects | [68] |
| Diallyl disulfide [Liposomes]                | Egg phosphatidylcholine, Dioleoyl Phosphatidyl Ethanolamine, and Cholesteryl Hemisuccinate                           | Promising strategy against DMBA-induced skin papilloma                              | [69] |
| Diallyl disulfide [Liposomes]                | Phosphatidylcholine  | Used in murine candidiasis treatment by decreasing residual fungal load             | [70] |
| Diallyl sulfide [Nanorods]                   | Egg white, Zinc Oxide  | Promising strategy in the treatment of dermatitis                                   | [71] |
| Diallyl sulfide [Liposomal gel]              | Phosphatidylcholine, Cholesterol, Carbopol 970, 974 and 980  | Superior herbal antifungal composition  | [72] |
| Allicin [Novel gel formulation]              | Dehydroxanthan gum, Tocopherol, Sodium Ascorbyl Phosphate, Polysorbate 20, Sodium hydroxymethylglycinate and Geranio | Promising strategy against bacterial infections                                     | [73] |
| Allicin [Polymeric nanoparticles]            | Gelatin, Glycyrhretinic acid   | Promising strategy for liver cancer therapy   | [74] |
| Allicin [Liposomal gel]                      | Egg phosphatidylcholine, Soya Lecithin, and Cholesterol  | Promising strategy for targeting of antifungal drugs                                | [75] |
| Allicin [Bilayer tablet]                     | Sodium starch glycolate, Polyvinyl pyrrolidone, Xanthan gum, Hydroxypropyl methylcellulose K-100                     | Used for effective treatment of hypertension  | [76] |
| Allicin [Nanocomposite hydrogel]             | Poly-(acrylic acid-co-acrylamide), Polyvinyl alcohol, Cloisite 15A   | Superior wound dressing materials   | [77] |
| Diallyl Trisulfide [Microemulsion]           | Cremophor EL   | Promising strategy for i.v. delivery of diallyl trisulfide                          | [78] |

## 5. Pre-clinical testing of garlic and its phytoconstituents for several therapeutic roles

Different phytoconstituents from garlic, their therapeutic activity, and *in-vivo* testing models are represented in Table 2.

**Table 2.** Pre-clinical testing models for investigation of therapeutic roles of phytoconstituents from garlic.

| Phytoconstituents            | Therapeutic role                        | Models/Activity  | Ref. |
|------------------------------|---|--|------|
| Thiocremonone                | Anti-inflammatory; anti-arthritis       | Tetradecanoyl-phorbol-13-acetate-induced ear edema; Carrageenan/mycobacterium butyricum-induced inflammatory/arthritis model | [79] |
| Diallyl disulfide            | Anti-arthritis                          | Complete Freund's adjuvant-induced arthritic rats  | [64] |
| Alliin, s-allyl cysteine     | Antioxidant                             | Trolox equivalent antioxidant capacity assay   | [11] |
| Diallyl sulfide              | Anti-oxidant/ Hepatoprotective          | Hepatic ischemia-reperfusion injury in a rat model   | [80] |
| Diallyl disulfide            | Anticancer                              | Human breast cancer cells in culture   | [81] |
| S-allyl-mercaptocysteine     | Anticancer                              | Gentamicin-induced rat kidney injury model   | [82] |
| Allicin                      | Antihypertensive                        | Tail-cuff method in hypertensive rats  | [83] |
| Propyl-propane thiosulfonate | Anti-inflammatory in intestinal colitis | Dinitrobenzene sulfonic acid and dextran sodium sulfate-induced mice models of colitis                                       | [84] |



| Phytoconstituents                | Therapeutic role                              | Models/Activity                                | Ref. |
|----------------------------------|---|--|------|
| Allicin                          | Anti-microbial; Anti-viral; Anti-inflammatory | Rodent malaria model Plasmodium yoelii 17XL    | [85] |
| Diallyl trisulfide               | Hepatoprotective; Antioxidant                 | Pentylenetetrazole-induced seizures mice model | [86] |
| Tulbaghia violacea (Wild garlic) | Anti-diabetic                                 | Diabetic rat model                             | [87] |

## 6. Clinical trials on garlic and its phytoconstituents in treatment of diseases

Clinical trials which have been previously conducted on phytoconstituents of garlic for the treatment of specific disease conditions have been collected from the official website of clinical trials (clinicaltrials.gov) and are enlisted in Table 3.

**Table 3.** Clinical trials on application of phytoconstituents of garlic for the treatment of disease.

| Study title  | Disease  | Sponsor  | Phase              | Ref. |
|--|--|--|--------------------|------|
| <b>Allicin</b>   |  |  |                    |      |
| Investigating the gut microbiota modulation effects of allicin for cardiovascular disease protection and establishing microbiota directed personalized nutrition guidance with novel humanized gnotobiotic mice model, microbial culturomics and metabolomic technique | Atherosclerosis  | National Taiwan University Hospital                              | Not available      | [88] |
| Garlic in hyperlipidemia caused by HAART   | HIV infections<br>hyper-cholesterolemia<br>hypertriglyceridemia<br>hyperglycemia | National Center for Complementary and Integrative Health (NCCIH) | Phase-2            | [89] |
| Identifying the anti-blood-clotting compounds in garlic  | Arteriosclerosis<br>intracranial arteriosclerosis                                | National Center for Complementary and Integrative Health (NCCIH) | Not Applicable     | [90] |
| Pirfenidone plus m-DDO gel in moderate and severe acne   | Acne vulgaris<br>superficial mixed comedonal and inflammatory                    | University of Guadalajara  | Phase-1<br>Phase-2 | [91] |
| Evaluation of post-operative pain after vital pulpotomy in primary molars using allium sativum oil versus MTA  | Deep caries  | Cairo University   | Not Applicable     | [92] |
| Dietary intervention in follicular lymphoma (KLYMF)  | Follicular lymphoma  | Oslo University Hospital   | Phase-2            | [93] |
| <b>Diallyl Sulfide</b>   |  |  |                    |      |
| Effectiveness of garlic oil in the treatment of arsenical palmer keratosis   | Chronic arsenic poisoning  | Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh   | Phase-2            | [94] |
| To evaluate the efficacy of DDB/garlic oil in patients with elevated transaminase chronic liver disease  | Chronic liver disease  | PharmaKing   | Phase-4            | [95] |
| Hormone estradiol replacement therapy additional herbals (WH)  | Menopause  | Triệu, Nguyễn Thị, M.D.  | Phase-4            | [96] |
| Study to evaluate efficacy and safety of PENNEL capsule in the patients with chronic liver disease   | Chronic Liver Disease  | PharmaKing   | Phase-3            | [97] |

| Study title   | Disease                 | Sponsor   | Phase              | Ref.  |
|---|-------------------------|---|--------------------|-------|
| Effect of DA-5515 (Circulan® Soft Cap.) in patients with chronic fatigue symptoms due to impaired blood circulation | Fatigue Symptom         | Dong-A Pharmaceutical                               | Phase-4            | [98]  |
| Study to evaluate efficacy, safety and tolerability of PENNEL capsule in the patients with chronic liver disease    | Chronic liver disease   | PharmaKing  | Phase-2            | [99]  |
| Diallyl Disulfide   |                         |   |                    |       |
| Efficacy of pirfenidone plus modd in diabetic foot ulcers   | Diabetic foot ulcers    | University of Guadalajara                           | Phase-1<br>Phase-2 | [100] |
| S-Allyl Cysteine  |                         |   |                    |       |
| Effect of a black garlic extract on cholesterol LDL levels (ESACTIVO)   | Cardiovascular diseases | Technological Centre of Nutrition and Health, Spain | Not applicable     | [101] |

## 7. Patents published about garlic's phytoconstituents in the management of diseases

Patents published on the applications of phytoconstituents of garlic to treat specific disease conditions have been collected from the WIPO and are enlisted in Table 4.

**Table 4.** Patents filed on the application of phytoconstituents of garlic for the treatment of disease.

| Publication No. | Title   | Purpose/Disease  | Applicant                                     | Date of Publication | Ref.  |
|-----------------|---|--|---|---------------------|-------|
| CN104187691     | Healthcare food capable of removing lead in the body  | Metabolite discharge of harmless elements from the body  | Qingdao Jinjiahui Food Co., Ltd.              | 10.12.2014          | [102] |
| US20160338971   | Nano co-encapsulation for the prevention and treatment of various disorders                                     | Anti-oxidants and chemo-preventive of various vascular, cardiovascular, oncological disorders, and infectious diseases | Shaker A. Mousa<br>Soad K. Jaouni             | 24.11.2016          | [103] |
| CN101524459     | Oil-in-water type garlic in-garlic oil sub-microemulsion as well as a method for preparing the same             | Adjuvant therapy of bacteria resistance, cardiovascular and cerebrovascular diseases and tumors                        | Shenyang Wanaipulide Pharm-tech Co., Ltd.     | 09.09.2009          | [104] |
| US20180168952   | Composition and application in baby lotion thereof  | Moisturizer for skin and reduces redness of skin allergy   | Shanghai Children's Nutrition Center Co., Ltd | 21.06.2018          | [105] |
| CN102727727     | Oil-in-water type sodium nitroprusside-garlic oil nanoemulsion antihypertensive drug                            | Antihypertensive (Half-life of sodium nitroprusside prolonged, and frequency of administration reduced)                | Northwest A&F University                      | 17.10.2012          | [106] |
| IN201711041514  | Topical formulation of capsate with aged garlic extract to prevent cold injuries                                | Prevention and treatment of cold injuries  | Lovely Professional University                | 23.11.2018          | [107] |
| US20060018982   | Topical application composition for preventing and treating pediculosis, method of elaboration and uses thereof | Prevention and therapy of pediculosis  | Roldan Vicente<br>Teofilo Barboza Juan Jose   | 26.01.2006          | [108] |



## 8. Conclusions

Garlic is a wonderful medicinal plant with abundant bioactive constituents like organosulfur compounds, allicin, s-allyl cysteine, S-allylmercaptocysteine, and diallyl sulfide, diallyl disulfide, and diallyl trisulfide. Through this review article, it has been found that garlic has versatile therapeutic potential in several illnesses such as cancer, obesity, diabetes, liver injury, hypertension, inflammation, viral infection as well as arthritis, and it has considerable immunomodulatory, anti-oxidant, and anti-microbial characteristics. This review article explains that the application of nanotechnology in the development of phytopharmaceuticals of garlic could provide superior therapeutic potential. Pre-clinical models, clinical trials, and patents briefly summarized in this review article about garlic's therapeutic applications and its phytoconstituents could bring readers more attention. Conclusively, this review gives prospective about garlic and provides effectual scientific proof for improved garlic utilization in human health and disease control.

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## Conflict of Interest

The authors declare no conflict of interest.

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