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Antioxidant, Immunomodulatory and Anti-Cancer Activities of *Sīr (Allium sativum L.) Bulb*-Unani Medicine for Promotion of Healthy Ageing

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Abstract

Sīr (garlic), species of the onion family, Liliaceae, is one of the most used plants in traditional medicine worldwide. More than 200 chemicals with diverse properties have been found in garlic extracts. Several garlic compounds were suggested to be efficient in improving various pathologies including certain types of cancer. It has *Mu'mmir* (Longevity promoting agent), *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for Innate heat), *Musakhkhin-i-Badan* (Calorific) *Muqawwī-i-Mi'da* (Stomachic), *Muqawwī-i-Bāh* (Aphrodisiac), *Muḥallil-i-Waram (*Anti-inflammatory*), Qāti' Akhlāt-i-Ghalīza* (Breaking agent for viscous humours), *Muqarreḥ* (Ulcerative), *Jālī* (Detergent), *Munaffith-i-Balgham* (Expectorant),*Musakkin* (Analgesic), *Mudirr-i-Bawl (*Diuretic*)* etc. properties. It is used in *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency), *Amrāḍ-i-Bārida Balghamiyya* (Cold phlegmatic disorders) such as *Laqwa (*Bell's palsy), *Istirkhā'* (Atony/flaccidity*), Ri'sha (*Tremor) *etc.*,*Fālij* (Hemiplegia), *Waja' al-Mafāṣil* (Polyarthritis),*'Irq al-Nasā* (Sciatica), *Ḍīq al-Nafas* (Bronchial Asthma), *Su'āl* (Cough) *Ḍu'f-i-Bāh* (Sexual debility), *Amrāḍ-i- Jild* (Skin Diseases like *Bahaq* (Pityriasis), *Baraṣ (*Vitiligo*)* etc. It showed Antioxidant, Immunomodulatory, Anti-ageing, Anti-Alzheimer's Disease, Anti-cancer, Anti-viral, Anti-inflammatory, Antibacterial, Anti-fungal, Antiprotozoal, Anti-hyperlipidemic, Cardio protective, Antihypertensive, Anti-obesity, Anti-Atherosclerotic, Antithrombotic etc. activities. In this paper, an attempt has been made to review the Unani pharmacological actions & therapeutic uses for a comprehensive understanding of the importance of bulb of *Sīr* (*Allium sativum* L.) for promotion of longevity and healthy ageing.

Keywords
Calorific, Antioxidant, Immunomodulatory, *Amrāḍ-i-Bārida Balghamiyya, Fālij.*

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Introduction	The drug of *Sīr* consists of bulb of *Allium sativum* L. (Family-Liliaceae), a perennial bulbous plant, cultivated as an important condiment crop in the country. The bulb is odoriferous and contains outer layers of thin sheathing leaves surrounding an inner sheath that encloses the clove. Often the bulb contains 10 to 20 cloves that are asymmetric in shape, except for those closest to the center. (Anonymous, 2008)  **Fig. *Bulb of Sīr***
Vernacular Name	English: Garlic; Hindi: *Lahasun*; Urdu: *Lahsan*, *Sīr*; Arabic: *Thawm, Fawm,*; Persian: *Sīr* (Khān, 2014; Ibn Sīnā,1987; Ibn Baytār, 1985; Ghani,YNM; Anonymous, 2008)
Temperament	*Ḥār* (Hot)[3] *Yābis* (Dry) [3] (Khān, 2014; Ibn Sīnā,1987; Kabīruddīn,2000)
Chemical Constituents	• Bulbs of *A. sativum* are reported to contain hundreds of phytochemicals including sulfur-containing compounds such as ajoenes (E-ajoene, Z-ajoene), thiosulfinates (allicin), vinyldithiins (2-vinyl-(4H) -1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), sulfides (diallyl disulfide (DADS), diallyl trisulfide (DATS)) and others that accounted 82% of the overall garlic sulfur content (*Al-Snafi,* 2013). • Alliin, the main cysteine sulfoxide is transformed to allicin by allinase enzyme after cutting off the garlic and breaking down the parenchyma (Zeng et al., 2017). S-propyl-cysteine-sulfoxide (PCSO), allicin and S-methyl cysteine-sulfoxide (MCSO) are the main odoriferous molecules of freshly milled garlic homogenates (Zeng *et al.,* 2017). PCSO can produce more than fifty metabolites depending on water content and temperature as well as allinase enzyme that can act on the mixture of MCSO, PCSO, and alliin to produce other molecules, such as allyl methane thiosulfinates, methyl methanethiosulfonate, and further corresponding thiosulfinates.(*El-Saber Batiha et al*., 2020). The main constituents present in bulb of *A. sativum* are volatile oil, allyl disulphide, dially disulphide, allin, allicin, mucilage, albumin etc. (Anonymous, 2008).
Pharmacological Actions	• *Mu'mmir* (Longevity promoting agent) • *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for Innate heat) • *Musakhkhin-i-Badan* (Calorific) • *Muqawwī-i-Mi'da* (Stomachic) • *Muqawwī-i-Bāh* (Aphrodisiac) • *Muḥallil-i-Waram (*Anti-inflammatory*)* • *Qāti' Akhlāt-i-Ghalīza* (Breaking agent for viscous humours) • *Muqarreḥ* (Ulcerative) • *Jālī* (Detergent) • *Munaffith-i-Balgham* (Expectorant) • *Musakkin* (Analgesic) • *Mudirr-i-Bawl (*Diuretic*)* (Khān, 2014; Ibn Sīnā,1987; *Ibn Baytār*, 1985; Al-Harawi,2002; Ghani,YNM; Anonymous, 2008)

Therapeutic Uses	• *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency) • *Amrāḍ-i-Bārida Balghamiyya* (Cold phlegmatic disorders) such as *Laqwa (*Bell's palsy), *Istirkhā'* (Atony/flaccidity)*, Ri'sha (*Tremor) *etc.* • *Fālij* (Hemiplegia) • *Waja' al-Mafāṣil* (Polyarthritis) • *'Irq al-Nasā* (Sciatica) • *Ḍīq al-Nafas* (Bronchial Asthma) • *Su'āl* (Cough) • *Ḍu'f-i-Bāh* (Sexual debility) • *Amrāḍ-i- Jild* (Skin Diseases like *Bahaq (*Pityriasis*), Baraṣ (*Vitiligo*)* (Khān, 2014; Ibn Sīnā,1987; Ibn Baytār, 1985; Al-Harawi,2002; Ghani,YNM; Anonymous, 2008;Kabīruddīn,2000)
Important Formulations	• *Ma'jūn Sīr* • *Majūn Sīr Alvi Khānī* • *Rawghan Sīr* (Anonymous, 2008)
Pharmacological / Clinical studies (evidence based)	**Antioxidant activity** • The Antioxidant potential garlic extracts were determined by using methanol, hexane and ethyl acetate at different time intervals (35, 50 and 65 min) followed by their polyphenols and flavonoid content determination. The result revealed that the methanolic extracts obtained at 50 min extraction time showed maximum total phenolics as 60.38±0.23 mg GAE/100g and flavonoids as 58.45±1.24 mg/100g. Similarly, the highest DPPH activity (61.59±1.58%) and β-carotene and linoleic acid potential (64.96±1.72%) were also observed for methanolic extract. (*Awan* et al. (2019) • *Shrestha* et al. (2016) carried out the study to evaluate the Antioxidant and antibacterial activities of fresh extracts of garlic and onion. Activities of enzymatic Antioxidants (superoxide dismutase and catalase) and non-enzymatic Antioxidant (ascorbic acid content) activities were measured and compared in between garlic and onion extracts. Superoxide dismutase and catalase activities in garlic were found noticeably high ($p < 0.05$) compared to onion but significantly reverse in case of the ascorbic acid content ($p < 0.05$). Likewise, six bacteria were chosen to study antibacterial activities of garlic and onion. The zones of inhibitions exhibited by the extracts against *B. cereus, S. aureus*, *Micrococcus* sp.*, E. coli, Klebsiella* sp. and *Proteus* sp. were compared with the reference antibiotic chloramphenicol (1%). Antibacterial activity of the garlic extracts singly and its mixture with onion extract in the ratio 1:1 against the tested bacteria were found significantly higher ($p < 0.05$) than the onion extract. They concluded that the Antioxidant activities of garlic are higher than onion and the antibacterial activities of garlic and its mixture are more potent than onion alone. • *Liu* et al. (2014) compared the Antioxidant activity of garlic aqueous and methanol extracts processed before and after boiling to mimic the cooking process. By testing the Anti-oxidant activities of the extracts in different chemical mimic systems *in vitro*, namely, ABTS [2, 2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid)] and DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging activities, reducing power, and metal chelating ability, they found the following data: (1) no significant difference was observed on the ABTS radical scavenging activities of garlic aqueous and methanol extracts before and after boiling process; (2) the reducing power of garlic aqueous and methanol extracts decreased by 25.9% and 14.1%, respectively, whereas the metal chelating activity of boiled garlic aqueous extracts increased by 54.7%; and (3) DPPH radical scavenging test may not be suitable to examine the garlic extracts. In addition, the ABTS radical scavenging activities of garlic extracts were very stable at pH ranges similar in human bodies, and both sulfhydryl and phenolic

compounds were probably responsible for the Antioxidant ability of garlic. The boiling process destroyed only a small part of garlic bio-ingredients related to Antioxidant activity properties.

Immunomodulatory Activity

- Moutia et al. (2018) reported different bioactive molecules and formulations of Garlic which were extensively probed in *in vitro* and *in vivo* studies to examine anti-inflammatory and immunomodulatory properties. One of the main mechanisms observed was through modulation of cytokine profiles and, on the other hand, direct instruction, and stimulation of immune cells. It was suggested that the garlic beneficial effects are attributed, in particular, to sulfur-containing compounds, some polyphenols, and flavonoids. The synergistic effect of the different compounds present in garlic preparations might be responsible for the biologic activities revealed in different pathological situations. However, the identification of the potential compound(s), which could eventually mediate efficient antitumor immunity, would be of major interest.
- The immunomodulatory properties of garlic could be useful in clinical applications since it enhances innate and specific cell immunity and also improves host resistance. It was also reported that allicin modulates T cells and adhesion molecules and exerts an inhibitory effect on NF-κB activation and hence prevents liver damage (*Bruck et al., 2005; Dorhoi et al.,* 2006)
- Immunomodulation is among innumerable biological activities of *A. sativum*. Aged garlic extract has showed superior immunomodula-tory properties over raw garlic extract. This effect of garlic is attributed to the transformed organosulfur compounds. Aged garlic fructans have recently showed to possess immunomodulatory activities *in vitro*. Garlic extract is concentration-dependently effective on the proliferation of interleukin (IL)-2 and interferon (INF)-γ gene expression of stimulated lymphocytes. The extracts reduced macrophage infection through induction of nitric oxide (NO) production *in vitro.*
- A study demonstrated that immune-mediated liver damage in mice can be prevented by allicin, probably because of its immunomodulatory effects on T cells and adhesion molecules and inhibition of NF-kappaB activation. Another observation indicated that allicin exerts an inhibitory immunomodulatory effect on intestinal epithelial cells and it may have the potential to attenuate intestinal inflammation. Allicin exerted an *in vitro* immunomodulatory effect on certain functions of the peripheral blood cells. (*El-Saber Batiha et al*., 2020).

Anti-Alzheimer's Disease Activity

- Alzheimer's disease (AD) is the main cause of dementia in the elderly with neurodegenerative and cerebrovascular disorders. Acetylcholinesterase (AChE) is the main enzyme that converts the acetylcholine (ACh) in the nervous system to acetate and choline. ACh depletion in the central nervous system has been involved in the pathophysiology noticed in AD; therefore, donepezil (AChE inhibitor) was effective in the management/prevention of AD. Surprisingly, oil from garlic bulbs suppressed AChE activity of cerebral cortex synaptosome and exhibits Antioxidant properties, thus, inhibiting AChE activity *in vitro* as well as their ability to scavenge diphenyl-1-picrylhydrazyl (DPPH) free radical. (Akinyemi et.al., 2018; Singh et al., 2010)
- *Borek* evaluated the neuroprotective effect of AGE using an animal model and showed that AGE protected brain from neurodegenerative diseases by preventing brain injury following ischemia, saving neurons toward apoptosis, and inhibiting oxidative death caused by β-amyloid. (Borek, 2006; Jackson et al.,2003)
- *Mbyirukira* and Gwebu reported that AGE or SAC inhibits the brain's frontal lobe degeneration, promotes memory and learning retention, and prolongs the lifespan. Based on the amyloid hypothesis, aggregated β-amyloid (Aβ) accumulation in the brain is believed to be the pathological factors that drive

the onset of AD. It has been suggested that the formation of the neurofibrillary tangles contain τ-protein and synaptic degradation caused by the imbalance consequences between Aβ clearance and Aβ production. (*Mbyirukiraet al*., 2003)

- *Haider* et al. reported that the prolonged garlic uptake is related to promoting the memory function by affecting the levels of the neurotransmitter, serotonin. The *in vivo* consumption of *A. sativum* extracts showed that it improves memory by eliminating free radicals that cause oxidative damage and inhibit AChE enzyme. It was noted that allicin inhibits AChE and butyrylcholinesterase (BuChE) enzymes (enzymes that break down neurotransmitter choline) which successively increased ACh concentration in the brain. Thus, delayed cognitive decline and dementia. (*Haider* et. al.,2008*; Mukherjee et.al.,2013)*
- Combination therapy of allicin with cholinesterase inhibitors (ChEIs) including rivastigmine, galantamine, and donepezil are now the most commonly used for the treatment of AD as they have the ability to correct the cholinergic deficiency seen with AD. Anti-oxidants such as tocopherol, selegiline, and ascorbic acid (vitamin C) were examined as a possible preventive therapy for AD, and they show delayed functional deterioration in AD patients. (*Hogan* et al.,2007; *Schmitt* et.al.,2004*)*
- *Millard* et al. reported that AChE incubated with allicin produced rapid inactivation that was concentration and time dependent. Many results showed concentration-dependent inhibition of bovine AChE by allicin complementing the previous finding. However, different cholinesterase inhibitors such as donepezil, rivastigmine, and tacrine are used to treat AD, and their side effects are becoming increasingly remarkable Therefore, the search for new derivatives extracted from the natural product with a dual function and lower side effects could be useful for patients with AD. Allicin is a small lipophilic molecule that can suppress BuChE and AChE, and therefore, enhances ACh concentration, which is decreased remarkably in AD patient's brains. Recently, allicin has also shown to have a protective effect on ischemic or traumatic neuronal damage controlled by apoptosis and oxidative stress pathways. (*Millard* et al., 2003; *Inglis*, 2002; *Jann* et.al.,2002; *Liu* et al.,2015)

Effect on Dyslipidemia

- In various experimental and clinical trials, the garlic was found to have an important effect on dyslipidemia by significantly decreasing serum TC, TG, and LDL levels and moderately increasing HDL cholesterol. (*Iweala* et al., 2005; *El-Saber Batiha et al*., 2020)
- *Sobenin* et al. revealed that garlic administration at a dose of 300 and 60 mg/day for 12 months and 12 weeks, respectively decreased TC, TG, and LDL while increased HDL. *(Sobenin et al.,2008; Sobenin, etal., 2010;;El-Saber Batiha et al., 2020)*
- *Ashraf* et al. reported that garlic tablets administration at a dose of 600 mg/day for 12 weeks in diabetic patients with dyslipidemia results in high HDL and low LDL and TC levels. (*Ashraf* et al.,2005; *El-Saber Batiha et al*., 2020)

Anti-cancer activity

- *Petrovic* et al. (2018) examined the molecular and cellular activities of a simple homemade ethanol-based garlic extract (GE) for the Anti-cancer activities in epidemiological studies. They found that GE inhibits growth of several different cancer cells *in vitro*, as well as cancer growth *in vivo* in a syngeneic orthotopic breast cancer model. Multiple myeloma cells were found to be especially sensitive to GE. The GE was fractionated using solid-phase extractions, and allicin was identified in one GE fraction; however, growth inhibitory activities were found in several additional fractions. These activities were lost during freeze or vacuum drying, suggesting that the main anti-cancer compounds in GE are volatile. The anti-cancer activity was stable for more than six months in −20

°C. They further reported that GE enhanced the activities of chemotherapeutics, as well as MAPK and PI3K inhibitors. Furthermore, GE affected hundreds of proteins involved in cellular signalling, including changes in vital cell signaling, cascades regulating proliferation, apoptosis, and the cellular redox balance. The data indicated that the reduced proliferation of the cancer cells treated by GE is at least partly mediated by increased endoplasmic reticulum (ER) stress.

- *Thomson and Ali* (2003) reported two major compounds in aged garlic, S-allylcysteine and S-allylmercapto-L-cysteine had the highest radical scavenging activity. In addition, some organosulfur compounds derived from garlic, including S-allylcysteine, have been found to retard the growth of chemically induced and transplantable tumors in several animal models. Therefore, the consumption of garlic may provide some kind of protection from cancer development.
- *Nouroz et al*. (2015) reported that compounds of garlic like *Alliin*, *Ajoene* and *Allicin* acts as efficient Anti-cancer agents.
- *Li et al.* (2018) suggested a possibility that the Anti-cancer property of garlic is more effective only when exposed directly to cancer cells than absorbed first by the normal epithelial cells of the gastrointestinal tract wall. They tested this possibility in two mouse models of highly aggressive malignancies that cannot yet be cured by conventional therapies: sarcoma 180- and EL4-induced lethal ascites. Daily oral gavages of raw garlic extract (RGE; equivalent to 100 mg wet weight) for 21 days failed to offer any meaningful effect in the mice with malignancies. However, the daily injection of the same amounts of the same materials for 21 days completely cured all the mice of cancer. This novel Anti-cancer activity of RGE was present entirely in the size fraction of the molecules smaller than 3000 Dalton rather than the larger molecules and was completely partitioned into the organic phase rather than into the aqueous phase. One half of the Anti-cancer activity was inactivated by heating at 100 °C for 10 min, suggesting that multiple components were concertedly involved. In a direct comparison, the RGE was significantly more effective in killing the cultured cancer cells *in vitro* than the extracts from other 21 raw vegetables and fruits. In cell culture, RGE killed a wide variety of different cancer cells regardless of species of origin and cell types. The most-effective way of treating cancer by RGE may be the direct injection instead of eating the cooked garlic.

Antiviral Activity

- The antiviral activity of garlic extracts has been evaluated against influenza B, human rhinovirus type 2, human cytomegalovirus (HCMV), Parainfluenza virus type 3, herpes simplex type 1 and 2, vaccinia virus, and vesicular stomatitis virus. Interestingly, in vivo experiment exhibited the antiviral activity of garlic extract, and they reported that garlic showed protective activity against influenza viruses by improving the production of neutralizing antibodies when given to mice and this activity was based on the presence of several phytochemicals namely, ajoene, allicin, allyl methyl thiosulfinate, and methyl allyl thiosulfinate. Allicin acts by preventing several thiol enzymes, while ajoene's antiviral activity was due to the prevention of adhesive interaction and fusion of leukocytes. Moreover, DATS was effective against the HCMV replication and viral immediate-early gene expression, and it acts by enhancing natural killer-cell (NK-cell) activity that destroys virus-infected cells. (El-Saber Batiha et al., 2020).

In addition to above activities:

- Bulb of *Allium sativum* has Anti-inflammatory activity, Anti-bacterial activity, Anti-fungal activity, Anti-protozoal activity, Anti-hyperlipidemic activity, Cardio-protective activity, Anti-hypertensive activity, Anti-obesity activity, Anti-Atherosclerotic activity, Anti-thrombotic activity. (El-Saber Batiha et al., 2020)

CONCLUSION:

Bulb of *Allium sativum* is rich in volatile oil, allyl disulphide, dially disulphide, allin, allicin, mucilage and albumin. It has *Mu'mmir* (Longevity promoting agent), *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for Innate heat), *Musakhkhin-i-Badan* (Calorific), *Qāti' Akhlāt-i-Ghalīza* (Breaking agent for viscous humours), *Jālī* (Detergent), *Mudirr-i-Bawl* (Diuretic) etc. properties. It is used in *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency), *Amrāḍ-i-Bārida Balghamiyya* (Cold phlegmatic disorders) such as *Laqwa (*Bell's palsy), *Istirkhā'* (Atony/flaccidity), *Ri'sha (*Tremor) *etc., Fālij* (Hemiplegia), *Waja'al-Mafāṣil* (Polyarthritis), *Amrāḍ-i- Jild* (Skin Diseases like *Bahaq (*Pityriasis*), Baraṣ (*Vitiligo*) etc.* It showed Antioxidant and free radical scavenging, Immunomodulatory, Anti-Alzheimer's Disease, Anti-inflammatory, Anti-viral, Anti-bacterial, Anti-fungal, Anti-protozoal, Anti-hyperlipidemic, Cardio-protective, Anti-hypertensive, Anti-obesity, Anti-Atherosclerotic, Anti-thrombotic etc. activities. Regular use of *Sīr* in diet in prescribed doses may help delay ageing process, strengthen body faculties, prevent and control chronic diseases like atherosclerosis, dyslipidemia, obesity, hypertension and thus ensure longevity and healthy ageing.

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