

***Kushta Jast*, a conventional herbo-mineral immunity booster tonic: potential use in COVID-19**

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ABSTRACT

Kushta Jast (KJ) is a unique herbo-mineral preparation of the *Unani System of Medicine* (USM) which is prepared by *taklis* (calcination) and prescribed by the practitioners of USM for the treatment of various ailments, including the respiratory ailments. It is used as *muqawwi* (tonic) to boost the immunity (*Muqawwi-i-badan*), and can increase the phagocyte activity of the immune cells, thereby, promoting the growth and spread of lymphocytes and increasing circulating antibodies to neutralize a harmful pathogen and reduce *humma* or body fever (*Dafi'-i-humma*). Incidentally, the principal mineral component of KJ, zinc, has been widely acknowledged for its beneficial influence on the immune function, and decrease the risk of developing serious respiratory illnesses. In this manuscript, we provide a glimpse of the literature on KJ and postulate its potential beneficial effects in respiratory infections, including COVID-19.

Keywords Unaniopathy, immunity, infection, virus, respiratory diseases, corona virus, SARS-CoV-2

1. INTRODUCTION

Kushta or calx is a fine powder prepared by the method of *taklis* (calcination) and used for the treatment of various ailments by the practitioners of the *Unani System of Medicine* USM, a tradition of Graeco-Arabic medicine which has its roots in the teachings of the Greek physician Hippocrates and Roman physician Galen, and developed by the Arabian and Persian physicians - *Rhazes*, *Avicenna*, *Al-Zahrawi*, and *Ibn Nafis*. The term *Kushta* is derived from the Persian word '*KUSHTAN*', meaning 'killed' or 'conquered'. *Kushtas* are unique USM preparations of plant, mineral or animal origin drugs which are most effective in small dosage forms and have a prompt action. These are used in various diseases, including common cold (Jagan N, 1981). However, in spite of the ancient nature of these preparations, modern scientific literature on calx is not much available, more likely due to a communication gap between the practitioners of the Unaniopathy (USM) and modern scientific researchers.

KushtaJast (KJ) is a preparation of *Bukan booti* and *Jast* (zinc, Zn) (Table 1). The herbal component of KJ, known as *Bukan booti* in USM and *Jalpapili* in Ayurveda (Scientific name *Phyla nodiflora* L., Synonym: *Lippia nodiflora* L., Family *Verbenaceae*) is a perennial creeper found throughout India. It is used in a number of Unani preparations as a cure for ailments

including cough, asthma, bronchitis and infections such as gonorrhoea. In USM, KJ is used as a cardiac tonic, brain tonic, antipyretic, aphrodisiac, stomachic, blood purifier, and as an immunity booster (Kalam MA, 2016; Khan HJ, 1950; Kareem B, 1960; Ghani N, 2011; Kabir al-Din, 2007; Zaki MM, 1890; Rafiq al-Din, 1985). Zn, which is the mineral component of the preparation, KJ, is present in the form of zinc sulfide, zinc carbonate and zinc oxide. When *Jast* (Zn) is heated in open air, it turns into oxide, and known as the flower of Zinc (Jagan N, 1981). Incidentally, Zn, the mineral component of KJ, positively influences the immune function, a property which has been extensively investigated by Prasad (2007b).

Zn is particularly important in respiratory infections, where the element has been reported to mitigate the symptoms of common cold, respiratory tract infection, pneumonia, HIV, and various other diseases, as summarized in Table 2. The presence of Zn in KJ may be a key reason for its beneficial effects in viral infections including the common cold and respiratory diseases. In this review article, we have attempted to summarize and analyze the existing literature on KJ and its major constituent Zn with an objective to provide literary evidence for the potential beneficial effects of KJ as a prophylactic preparation in COVID-19.

Table 1. Main ingredients of *Kushta Jast* or zinc calx prepared by the conventional method.

| Sl. No | Key ingredients | Scientific name | Part used | Quantity |
|--------|--------------------|------------------------------------|---------------------|----------|
| 1 | <i>Jast</i> | Zinc | Fine powder | 10 g |
| 2 | <i>Bukan booti</i> | <i>Phyla nodiflora</i> (L.) Greene | Paste of whole herb | 60 g |

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Table 2. Beneficial effects of zinc in infectious diseases

| Sl.No. | Disease condition | Effect of zinc |
|--------|------------------------------|---|
| 1 | Common cold | Reduce the duration and severity of symptoms (Hulisz D, 2004; Prasad AS, 2000; Turner RB, 2000; Petrus EJ, 1998; Mossad SB, 1996; Godfrey JC, 1992; Eby GA, 1984). |
| 2 | Respiratory tract infections | Reduce acute respiratory infections, upper respiratory tract infection, and increase the recovery rate (Martinez ENS, 2015; Malik A, 2014; Shah UH, 2013; Sazawal S, 1998). |
| 3 | Pneumonia | Zn deficiency increase the risk of pneumonia (Lassi ZS, 2016; Bhandari N, 2002; Sazawal S, 1998). |
| 4 | Diarrhea | Zn supplementation reduces the risk of diarrhea in young children (Rosado J, 1997; Sazawal S, 1997). |
| 5 | HIV | In HIV, Zn reduces the viral load and increase CD4+ and CD8+ count (Zazzo JF, 1989; Asdamongkol N, 2013; Lodha R, 2014). |
| 6 | Hepatitis C virus | Reduce aminotransferases, α -fetoprotein, and decreased viral RNA (Murakami Y, 2007; Kawaguchi A, 2015). |
| 7 | Malaria | Prevent malaria morbidity, reduces the malaria attack and fever (Shankar AH, 2000; Bates CJ, 1993). |
| 8 | Leprosy | Reduces the incidence and severity of erythema <i>nodosum leprosum</i> and reduce the bacterial load (Mathur NK, 1983; Mathur NK, 1984). |

2. KJ: Method of preparation, properties and actions

2.1 Conventional method for preparation, chemical and physical properties

KJ is a herbo-mineral preparation containing Zn (Table 1), a mineral known by various synonyms in USM: *Ruye Tutiya, Ruh Tutiya, Shubbah, Kharseen, Rumi Tutiya, Qasdeer, Qaitoon, Atarad, Kharchini, Jasad* (Khan HJ, 1950; Kareem B, 1960; Ghani N, 2011; Zaki MM, 1890; Husain TS, 1981; Fazlullah M, 1877; Ali MN, 1860; Kabir al-Din, 1955). KJ can be prepared from Zn by various methods described in Unani literature (Jagan N, 1981; Kareem B, 1960) by a process called *Taklis* as described earlier (Jagan N, 1981; Khan HJ, 1950; Kareem B, 1960). Briefly, Zn granules are powdered and mixed with a paste of *Bukan booti*. The mixture is covered with 100 g cotton and then placed in an earthen disc by a specialized conventional sealing process of *Gil-e-hikmat* in which the mixture is prepared by mixing clay and cotton till a uniform paste is obtained. Finally, the closed vessel is heated by a fire of cow dung cakes (10 kg). After complete combustion, the material is grounded to fine powder and filtered through a 160-number mesh (Anonymous, 2006).

Zn obtained from mines is not pure but mixed with *gandhak* (sulphur) as zinc sulphide (zinc blande), or with carbon as zinc carbonate (Jagan N, 1981; Kareem B, 1960; Ghani N, 2011; Kabir al-Din, 1955). It is bluish white in color (Kareem B, 1960) with an astringent taste (Zaki MM, 1890) or tasteless (Ghani N, 2011; Fazlullah M, 1877). KJ is white, but turns yellowish on heating (becoming white when cooled). It is light weight, does not dissolve in water and used orally. It is important to note that the *Kushtas* have a high dissolution rate (readily distributed in the body), have a quick and powerful action at a low dosage (when compared with other conventional dose levels), and have a longer shelf life (Jagan N, 1981; Kareem B, 1960; Aziz N, 2002).

2.2 Pharmacological properties and therapeutic uses

Kushtas (calxs) have mostly *muqawwi* (tonic) actions, apart from many other specific actions and therapeutic uses. KJ is used in many ailments as *muqawwi* (tonic) to strengthen the body immunity (Table 3). *Muqawwi-i badan* (immunity booster) is a key activity of KJ which may explain many of its pharmacological properties. Therapeutically, KJ is used for the

management of diseases on the basis of its actions like *Hummiyat* (Fevers), *Jarayan* (spermatorrhoea), *Zu'fal-Bah* (loss of libido), *Sur'a al-Inzal* (premature ejaculation), *Riqqat al-Mani* (low viscous semen), *Sayalan al-Rahim* (leucorrhoea), *Dama* (bronchial asthma), *Nafth al-Dam* (hemoptysis), *Kathra al-Ihtilām* (excessive nocturnal emission), *Qillat-i-Dam* (anemia), *Dhayābītus* (diabetes), *Sual* (cough), *Waja' al-Mafasil* (polyarthritis), *Ātshak* (syphilis), *Judhām* (leprosy), *Ra'sha* (tremors), *Sill* (phthisis), *Yaraqan Asfar* (jaundice), *Zahīr* (dysentery), *Ishāl* (purgation) and *Sahj al-Am'ā'* (abrasion in intestine) (Jagan N, 1981; Kabir al-Din, 1955; Kabir al-Din, 2007; Kareem B, 1960; Khan HJ, 1950; Ghani N, 2011). It is beneficial in weakness caused by heavy work and exertion and is also used in *Amrād-i-qalb* (cardiac ailments). It prevents menstrual blood loss (Jagan N, 1981) and has been found useful in *Amrād-i-kabid* (liver ailments) and *Amrād-i-mi'da* (stomach ailments) as tonic (Kareem B, 1960).

When used with *Ajwain* (*Trachyspermum ammi* L.) and *Laung* (*Eugenia caryophyllus* Bull.), KJ can cure fever with rigor. It cures bronchial asthma (*Dama*) when taken orally with honey (6 g fresh juice, heat it then cooled, followed by adding 6 ml honey and 125 mg KJ). KJ is a blood purifier when taken with *Maveez munaqqa* (*Vitis vinifera* L.). It can cure *Sozāk* (gonorrhoea) when taken with Sandal oil (*Santalum album* L.). It clears urine and increase frequency of micturition if taken with *Gokhru* (*Tribulus terrestris* L.). KJ prevents bleeding if taken with *Dammul akhwain* (*Dracaean cinnabari* Balf.). It can prevent bleeding with stool when taken with *Murabba* or *Sharbat of belgiri* (*Aegle marmelos* Corr.). With *Tukhm konch* (seeds of *Mucuna pruriens* Baker.) and *Misri* (sugar), KJ cures *Jarayan* (spermatorrhoea) (Ghani N, 2011). Externally also, KJ can be used alone or mixed with some other drugs as an ingredient in ointments for wounds and ophthalmic conditions. It is very useful to seize oozing of secretions from the wounds and ulcers due to its desiccant action (*Mujaffif-i-Quruh*) (Ghani N, 2011; Kabir al-Din, 2007; Kabir al-Din, 1955). In eye diseases (*Amrad chashm*), KJ is used in *Surma* (corrylium) or alone as a micro fine powder to apply directly into the eye (Jagan N, 1981; Khan HJ, 1950; Kareem B, 1960; Ghani N, 2011; Kabir al-Din, 2007; Kabir al-Din, 1955). KJ is *Muhallil waram* (resolvent to inflammation) (Ghani N, 2011; Fazlullah M, 1877; Zaki MM, 1890) and has *Qabid* (astringent) action also (Ghani N, 2011; Kabir al-Din, 2007; Kabir al-Din, 1955; Rafiq al-Din, 1985).

Table 3. Uses of KJ in USM

| Use in Unani medicine | Equivalent term/ description in English |
|-----------------------|--|
| Dafi'a Tashannuj | Antispasmodic (Ghani N 2011) |
| Dafi'a Humma | Antipyretic (Kabir al-Din 2007; Rafiq al-Din 1985; Kabir al-Din 1955) |
| Dafi'a Khafaqan | Relieve palpitation (Ghani N 2011; Ali MN 1860) |
| Mughalliz-i-Mani | Increases the viscosity of the semen (Kabir al-Din 2007; Rafiq al-Din 1985; Kabir al-Din 1955) |
| Mumsik-i-Mani | Retentive of semen (Kareem B 1960; Rafiq al-Din 1985; Kabir al-Din 1955) |
| Muqawwi Qalb | Cardio-tonic (Khan HJ 1950; Ghani N 2011; Zaki MM 1890; Ali MN 1860; Fazlullah M 1877) |
| Muqawwi-i-Badan | Immunity booster (Jagan N, 1981) |
| Muqawwi-i-Bah | Aphrodisiac (Jagan N, 1981; Kareem B 1960) |
| Muqawwi-i-Dimagh | Brain tonic (Jagan N, 1981) |
| Muqawwi-i-Mi'da | Stomachic (Ghani N 2011; Zaki MM 1890; Ali MN 1860; Fazlullah M 1877) |
| Musaffi-i-Dam | Blood purifier (Kareem B 1960) |
| Musakkin | Neutralize the heat of humours (Kabir al-Din 1955) |

2.3 Use of KJ in common cold and respiratory diseases

The concept of *Muqawwi* (tonics) is unique to USM. Tonics are nontoxic natural substances which can improve and maintain the human health when used regularly. They tone up the organs and improve the body functions. In USM, the idea is to strengthen the body as it has the power to fight any adverse situation leading to disease condition. *Muqawwi-i-badan* (immunity booster) and *Dafi'a humma* (antipyretic) are two important properties of KJ reported in literature (Jagan N, 1981; Khan HJ, 1950; Ghani N, 2011; Zaki MM, 1890; Ali MN, 1860; Fazlullah M, 1877). Although there is no mention of a direct antiviral action of KJ in Unani literature, it is reported to reduce the body fever (*Humma*), which is a symptom of viral infection (Jagan N, 1981; Kareem B, 1960; Kabir al-Din, 2007; Kabir al-Din, 1955). It is important to understand that the Unani system is based on holism, and whole body is treated as a unit by improving the body's immune mechanism by some methods or drugs. KJ as a tonic improves the immunity, and hence may be considered as a prophylactic traditional medicine with potential use in SARS-Cov-2 infection or COVID-19.

Incidentally, Zn, the mineral component of KJ, has also been found to influence body organs and body functions (Lambert SA, 2018; Andreini C, 2012). Zn is essential for cellular processes which include diverse cellular functions as wide as interleukin-2 (IL-2) production, DNA synthesis and RNA transcription (Prasad AS, 2007a; Overbeck S, 2008). An adult human body contains only about 2 g of Zn and approximately 10 to 18 µM plasma Zn content (Rukgauer M, 1997). Daily Zn requirement is about 10-15 mg/d, which may increase up to 50% during pregnancy and lactation. Fish, meat, egg, milk and nuts are key dietary sources of Zn (Satyanarayana U, 2013). Intake of high cereal protein, which is rich in phytate which makes Zn unavailable for absorption, hampers Zn absorption and causes of Zn deficiency, which may be mild to severe. Recurrent infections due to cell-mediated immune dysfunction have been linked to the Zn deficiency (Prasad AS, 2007b). Zn deficiency affects the

activity of the natural killer (NK) cell (Beck FW, 1997a; Beck FW, 1997b). Even a mild Zn deficiency can affect clinical, biochemical and immunological functions adversely. Zn clinically improves symptom of common cold, respiratory infections and pneumonia. *In vitro* and *in vivo* studies on viral infections suggest a direct antiviral action of Zn. Zn improves IFN- α production (antiviral) (Cakman I, 1997).

It has been found to reduce the viral titer and plaque count in respiratory syncytial virus infection (Suara RO, 2004). Zn is effective in HCV, possibly by inhibiting RNA polymerase and replication (Ferrari E, 1999; Himoto T, 2007). Zn can inhibit herpes simplex virus replication through interfering with proteasome function and NF- κ B activation (Qiu M, 2013). It can inhibit the human papilloma virus by stimulation of pro-viral transcription activity, reversed by EVER2 (Lazarczyk M, 2008). Zn can ameliorate the effect of HIV infection and interferon production (Zazzo JF, 1989). Several clinical studies suggest the antiviral effect of Zn against rhinovirus (Korant BD, 1974; Korant BD, 1976; Hung M, 2002). Zn can reduce the duration, severity of the symptoms related to common cold (Prasad AS, 2000; Turner RB, 2000; Petrus EJ, 1998; Mossad SB, 1996; Godfrey JC, 1992; Eby GA, 1984). We do believe the antiviral effect of Zn against SRAS-CoV-2 infection, which is presently under investigation (Thailand MN, 2020). The presence of Zn in KJ provides a clue to its *Muqawwi-i badan* (immune boosting) activity, and its potential use as a tonic (*muqawwi*) in SRAS-CoV-2 infection.

3. DISCUSSION

Bukan booti (*Phyla nodiflora* L.) is a medicinal herb (creeper) found throughout Indian subcontinent. In USM, the *Bukan booti* is used in various ailments such as asthma, bronchitis, knee joint pain, gonorrhoea, hepatitis, fever and in infectious disease (Ghani N, 2011). The *booti* possess various pharmacological properties

and is used as antimicrobial and antifungal (Arumanavagam S, 2015). It has the anti-inflammatory property, antipyretic and analgesic activity (Ahmed F, 2004) and is antihypertensive (Gadhvi R, 2012). It has been studied for its antioxidant, antitumor (Durairaj AK, 2009), antidiabetic and hypolipidemic activity (Balamurugan R, 2011), as well as sedative, anticonvulsant and anxiolytic effects (Kumaresan P, 2011). In Unani literature, the therapeutic actions of *Bukan booti* are given as *Musakkīn Josh-e Khoon* (neutralize blood), *Musaffī-i-Dam* (blood purifier), *Nafī'a Bawāsīr* (useful in piles/hemorrhoid), *Mudīrr-i-Bawl* (diuretic) (Kabir al-Din, 2000; Kabir al-Din, 2007) and *Dafī'a Fasād-i Safra* (neutralize bile) (Ali A, 1914). The *booti* is used in different forms which include infusion with *Siyah mirch* (*Piper nigrum* L.), used for detoxification of the blood, *Bawāsīr* (bleeding piles) and *Ru'af* (epistaxis) (Ali A, 1914; Kabir al-Din, 2000; Kabir al-Din, 2007). It is useful in *'Ushr al-Bawl* (dysuria) and *Hasāh al-Mathāna* (cystolithiasis) (Ali A, 1914; Arshi MMN, 1929; Kabir al-Din, 2000; Ali MN, 1860; Fazlullah M, 1877; Kabir al-Din, 2007; Zaki MM, 1890). Its use has been indicated in *Hummayat* (fevers) due to *Ufunat* (infection) and predominance of *Balgham* (phlegm). *Bukan booti* is used in cough, *'Sozāk* (gonorrhoea) (Ali A, 1914; Arshi MMN, 1929; Ali MN, 1860; Fazlullah M, 1877; Zaki MM, 1890), *Qula* (stomatitis) (Ali A, 1914) and externally as a paste to resolve inflammation (*Muhallil Waram*) and ripen boils (Ali MN, 1860; Fazlullah M, 1877; Zaki MM, 1890).

According to the Unani system of medicine the mixing of different herbs in the preparation of calx is commonly employed to get best *Kushta*. Although the reason for mixing different drugs in different *Kushtas* is not clearly mentioned, but it may be concluded that these herbs have some useful effects on *Kushtas*; either their effects got mixed with the *Kushta*, or they may reduce adverse effects or enhance the efficacy of *Kushta*. In case of KJ, *Bukan booti* is used to either enhance the efficacy or reduce toxicity and make the calx more efficacious. Zn in KJ has a multiple of effects on the cells of the immune system. Besides improving the interferon (antiviral) production, which upregulates the MHC class 1 antigen expression (Cakman I, 1997; Prasad AS, 2007b), it affects the overall immune system. Some of the effects of KJ listed in Table 3 may be partly attributed to Zn effect. In fact, Zn deficiency has been reported to affect the immune cells including the NK cells, macrophages and neutrophils, where KJ as whole may add up to the beneficial effect on the immune system.

Incidentally, Zn deficiency is also reported to adversely affect the phagocytosis (Shankar AH, 2000) and decrease the production of TNF- α (which plays a role in phagocytosis) (Kim YJ, 2009). KJ, due to the presence of Zn as its mineral component, may help reduce the virus load and can be beneficial in SARS-CoV-2 infections. Thymulin (which requires Zn) binds to T cells and promote its functions (IL-2 production and suppressor functions) (Prasad AS, 1988; Beck FW, 1997b). Zn deficiency can stress the macrophages and monocytes, and also shift the oxidant/antioxidant balance favorably (Prasad AS, 2004; Prasad AS, 2007a). Reprogramming of the immune system has been correlated with chronic zinc deficiency (Fraker PJ, 2004; Prasad AS, 2007b). An enhanced expression of IL-2 and its receptors via NF- κ B is another beneficial effect of Zn in infections (Serfling E, 1995). Taken together, Zn supplementation does not only enhance the various immune processes such as phagocytosis and intercellular killing, but also upregulates the MHC class I antigen for better recognition of viral proteins and nucleic acid. Presence of *Bukan booti* in KJ add up to these beneficial effects of Zn, and may bring down the toxic effect, if any, besides improving the bioavailability as calx are known for their rapid action at low dosage. These potential

beneficial effects of KJ make it a potential candidate at least as a prophylactic agent in SARS-CoV-2 infection. KJ may be considered as a conventional remedy for the prophylaxis of COVID-19.

4. CONCLUSION

Kushta Jast is a unique Unani herbo-mineral preparation of *Bukan booti* and *jast* or zinc prepared by the conventional method of *Gil-e-hikmat*. It is used as a *muqawwi* (tonic) to tone up the organs and improve the body function, including the immune function (*Muqawwi-i-badan*) and antipyretic (*Dafī'a humma*). Although there is no direct mention of antiviral activity in Unani system of medicine, *Kushta jast* reduces the body fever (*humma*), and its mineral component, zinc, is widely acknowledged to improve the immune function and help fight viral infections. Going by the Unani concept of holism, where whole body is treated as a unit and where the idea is to strengthen the entire body, *Kushta jast* is proposed as a prophylactic traditional preparation that may be effective against SARS-Cov-2 infection/ COVID-19. Additionally, calx (*Kushta*) is effective at low dosage and has prompt action.

CONFLICT OF INTEREST

Authors declared that there was no conflict of interest.

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REFERENCES

- Ahmed F, Selim MS, Das AK, Choudhuri MS. Anti-inflammatory and antinociceptive activities of *Lippia nodiflora* Linn. *Pharmazie*. 2004;59(4):329-30.
- Ali A. *Maqalat-e-Ahsani*. (Kanpur, India: Dar Matba, Nami Nawal Kishore), 1914.
- Ali MN. *Nasirul Moalijeem*. (Lucknow, India: Matba Alwi Muhammad Ali Bakhsh), 1860.
- Andreini C, Bertini I. A bioinformatics view of zinc enzymes. *J Inorg Biochem*. 2012;111:150-156.
- Anonymous. *National Formulary of Unani Medicine*. Part-I. India: Ministry of Health and Family Welfare, Govt. of India, 2006.
- Arshi MMN. *Mufradat-e-Arshi*. (Lahore, Pakistan: Kutubkhana Arshi Dhanola, Pratap Press), 1929.
- Arumanavagam S, Arunmani M. Hepatoprotective and antibacterial activity of *Lippia nodiflora* Linn. against lipopolysaccharides on HepG2 cells. *Pharmacogn Mag*. 2015; 11(41): 24–31.
- Asdamongkol N, Phanachet P, Sungkanuparph S. Low plasma zinc levels and immunological responses to zinc supplementation in HIV-infected patients with immunological

- discordance after antiretroviral therapy. *J Infect Dis.* 2013; 66:469-474.
- Aziz N, Gilani AH, Rindh MA. Kushta(s): unique herbo-mineral preparations used in South Asian traditional medicine. *Med Hypotheses.* 2002;59(4):468-472.
- Balamurugan R, Duraipandiyan V, Ignacimuthu S. Antidiabetic activity of γ -sitosterol isolated from *Lippia nodiflora* L. in streptozotocin induced diabetic rats. *Eur J Pharmacol.* 2011;667(1-3):410-418.
- Bates CJ, Evans, PH, Dardenne M, et al. A trial of zinc supplementation in young rural Gambian children. *Br J Nutr.* 1993;69(1):243-255.
- Beck FW, Kaplan J, Fine N, et al. Decreased expression of CD73 (ecto-5'-nucleotidase in the CD8+ subset is associated with zinc deficiency in human patients. *J Lab Clin Med.* 1997a;130(2):147-156.
- Beck FW, Prasad AS, Kaplan J, et al. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *Am J Physiol.* 1997b; 272(6 Pt 1):E1002-E1007.
- Bhandari N, Bahl R, Taneja S et al. Routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomized controlled trial in an urban slum. *BMJ.* 2002;324(7350):1358.
- Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon- α by leukocytes from elderly persons. *J Interferon Cytokine Res.* 1997;17(8):469-472.
- Durairaj AK, Mazumdar UK, Gupta M, Selvan VT. Effect on inhibition of proliferation and antioxidant enzyme level of *Lippia nodiflora* in EAC cell line treated mice. *J Comp IntegMed.* 2009; 6:713-714.
- Eby GA, Davis DR, Halcomb WW. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. *Antimicrob Agen Chemother.* 1984;25:20-24.
- Fazlullah M. Makhzanul Mufradat Maroofba Jamia-ul-Advia. (Lucknow, India: Dar Matba Anwar Muhammad), 1877.
- Ferrari E, Wright-Minogue J, Fang JW, et al. Characterization of soluble hepatitis C virus RNA-dependent RNA polymerase expressed in Escherichia coli. *Virology.* 1999;73(2):1649-1654.
- Fraker PJ, King LE. Reprogramming of the immune system during zinc deficiency. *Annu Rev Nutr.* 2004; 24:277-298.
- Gadhvi R, Mishra GJ, Reddy MN, Nivserkar M. Antihypertensive efficacy of *Lippia nodiflora* - whole plant on uninephrectomized doca - salt hypertensive rats. *IOSR J Pharm.* 2012; 2:24-28.
- Ghani N. Khazainul Advia. (New Delhi, India: Idara Kitabul Shifa), 2011.
- Godfrey JC, Sloane BC, Smith DS, et al. Zinc gluconate and the common cold - a controlled clinical-study. *J Int Med Res.* 1992;20(3):234-246.
- Himoto T, Hosomi N, Nakai S, et al. Efficacy of zinc administration in patients with hepatitis C virus-related chronic liver disease. *Scand J Gastroenterol.* 2007;42(9):1078-1087.
- Hulisz D. Efficacy of zinc against common cold viruses: an overview. *J Am Pharm Assoc.* 2003. 2004; 44(5):594-603.
- Hung M, Gibbs CS, Tsiang M. Biochemical characterization of rhinovirus RNA-dependent RNA polymerase. *Antiviral Res.* 2002; 56(2): 99-114.
- Husain TS. Lughat-e-Kishori. (Lucknow, India: Matba Munshi Tejkumar Pvt. Ltd.), 1981.
- Jagan N. Ilm-wa-Amal Kushtajaat. (Chandosi, India: Taksal Ayurvedic Pharmacy), 1981.
- Kabir al-Din HM. [(1894-1976 AD)]. 5th ed. Kitabul Advia. (Hyderabad, India: Daftar al-Masih, Bazar Nur al-Umara), 1955.
- Kabir al-Din HM. [(1894-1976 AD)]. Ilmul Advia Nafeesi. (New Delhi, India: Aijaz Publishing House), 2007.
- Kabiral-Din HM. [(1894-1976 AD)]. Makhzanul Mufradat. (Deoband, India: Faisal Publication), 2000.
- Kalam MA, Ahmad G, Munshi YI, Ahmad S. *Bukan Booti (Lippia nodiflora L.) - A Lesser Known Unani Drug.* *Hipp. J. Unani Med.* 2016; 11(4):131-139.
- Kareem B. Miftahul Khazain Darbayan Iksir-wa-Rasayan. (Lahore, Pakistan: Darul Kutub Rafiqul Atibba), 1960.
- Kawaguchi A, Nagao Y, Abe K, et al. Effects of branched-chain amino acids and zinc-enriched nutrients on prognosticators in HCV-infected patients: A multicenter randomized controlled trial. *Mol Med Rep.* 2015;11(3):2159-2166.
- Khan HJ. Al-Hikmat. (Delhi, India: Hindustani Dawakhana), 1950, pp.45-46.
- Kim YJ, Kang JH, Yang MP. Zinc Increases the phagocytic capacity of canine peripheral blood phagocytes invitro. *Vet Res Commun.* 2009;33(3):251-261.
- Korant BD, Butterworth BE. Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides. *J Virol.* 1976;18(1):298-306.
- Korant BD, Kauer JC, Butterworth BE. Zinc ions inhibit replication of rhinoviruses. *Nature.* 1974;248(449):588-590.
- Kumaresan P, Thirupati T, Vijay C. Neuropharmacological activity of *Lippia nodiflora* Linn. *Pharmacog Res.* 2011;3(3):194-200.
- Lambert SA, Jolma A, Campitelli LF, et al. The human transcription factors. *Cell.* 2018;172(4):650-665.
- Lassi ZS, Moin A, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. 2016;12(12):CD005978.
- Lazarczyk M, Pons C, Mendoza JA, et al. Regulation of cellular zinc balance as a potential mechanism of EVER mediated protection against pathogenesis by cutaneous oncogenic human

- papillomaviruses. *J Exp Med*. 2008;205(1):35-42.
- Lodha R, Shah N, Mohari N, et al. Immunologic effect of zinc supplementation in HIV-infected children receiving highly active antiretroviral therapy: a randomized, double-blind, placebo-controlled trial. *J Acquir Immune Defic Syndr*. 2014;66(4):386-392.
- Malik A, Taneja DK, Devasenapathy N, et al. Zinc supplementation for prevention of acute respiratory infections in infants: a randomized controlled trial. *Indian Pediatr*. 2014;51(10):780-784.
- Martinez-Estevéz NS, Alvarez-Guevara AN, Rodriguez-Martinez CE. Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: a 12-month randomized controlled trial. *Allergol Immunopathol Madr*. 2016;44(4):368-375.
- Mathur NK, Bumb RA, Mangal HN, et al. Oral zinc as an adjunct to dapsone in lepromatous leprosy. *Int J Lepr OthMyc Dis*. 1984;52(3):331-338.
- Mathur NK, Bumb RA, Mangal HN. Oral zinc in recurrent erythema nodosum leprosum reaction. *Lepr Ind*. 1983;55(3):547-552.
- Mossad SB, Macknin ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold - a randomized, double-blind, placebo-controlled study. *Ann Intern Med*. 1996;125(2):81-88.
- Murakami Y, Koyabu T, Kawashima A, et al. Zinc supplementation prevents the increase of transaminase in chronic hepatitis C patients during combination therapy with pegylated interferon alpha-2b and ribavirin. *J Nutr Sci Vitaminol*. (Tokyo). 2007;53(3):213-218.
- Overbeck S, Rink L, Haase H. Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. *Arch Immu Ther Exp*. 2008;56: 15-30.
- Petrus EJ, Lawson KA, Bucci, LR, Blum K. Randomized, double masked, placebo-controlled clinical study of the effectiveness of zinc acetate lozenges on common cold symptoms in allergy-tested subjects. 1998;59(9):595-607.
- Prasad AS, Bao B, Beck FW, Sarkar FH. Anti-oxidant effect of zinc in humans. *Free Radic Biol Med*. 2004;37(8):1182-1190.
- Prasad AS, Beck FW, Bao B, et al. Zinc supplementation decreases incidence of infections in the elderly: Effect of zinc on generation of cytokines and oxidative stress. *Am J Clin Nutr*. 2007a; 85(3):837-844.
- Prasad AS, Fitzgerald JT, Bao B, et al. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate-a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2000; 133:245-52.
- Prasad AS, Meftah S, Abdullah J, et al. Serum thymulin in human zinc deficiency. *J Clin Invest*. 1988;82(4):1202-1210.
- Qiu M, Chen Y, Chu Y, et al. Zinc ionophores pyrithione inhibits herpes simplex virus replication through interfering with proteasome function and NF- κ B activation. *Antiviral Res*. 2013;100(1):44-53.
- Rafiq al-Din HM. *Kanzul Advia Mufrada*. (Aligarh, India: University Publication Unit), 1985.
- Rosado J, Lopez P, Monoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. *Am J Clin Nutr*. 1997;65(1):13-19.
- Rukgauer M, Klein J, Kruse-Jarres JD. Reference values for the trace elements copper, manganese, selenium, and zinc in the serum/plasma of children, adolescents, and adults. *J Trace Elem Med Biol*. 1997;11(2):92-98.
- Satyanarayana U, Chakrapani U. *Biochemistry*, 4th ed. (New Delhi, India: Elsevier), 2013.
- Sazawal S, Black R, Bhan M, et al. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea - a community-based, double-blind, controlled trial. *Am J Clin Nutr*. 1997;66(2):413-418.
- Sazawal S, Black RE, Jalla S, et al. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. *Pediatrics*. 1998;102(1 Pt 1):1-5.
- Serfling E, Avots A, Neumann M. The architecture of the interleukin-2 promoter: a reflection of T-lymphocyte activation. *Biochim Biophys Acta*. 1995; 1263(3):181-200.
- Shah UH, Abu-Shaheen AK, Malik MA, et al. The efficacy of zinc supplementation in young children with acute lower respiratory infections: a randomized double-blind controlled trial. *Clin Nutr*. 2013;32(2):193-9.
- Shankar AH. Nutritional modulation of malaria morbidity and mortality. *J Infect Dis*. 2000;182 Suppl 1:S37-S53.
- Suara RO, Crowe JE Jr. Effect of zinc salts on respiratory syncytial virus replication. *Antimicrob Agents Chemother*. 2004; 48(3):783-790.
- Thailand Medical News. COVID-19 Supplements: Australian Researchers Start First Clinical Trial to Test Effects of Intravenous Zinc in COVID-19 Patients. 2020. Available at: <https://www.thailandmedical.news/news/covid-19-supplements-australian-researchers-start-first-clinical-trial-to-test-effects-of-intravenous-zinc-in-covid-19-patients>. (Accessed on 27th May 2020).
- Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis*. 2000;31(5):1202-1208.
- Zaki MM. *Makhzan-ul-Mufrida Maroofba Khawasul Adviya*, 2nd ed. (Saharanpur, India: Sheikh Muhammad Yameen Tajir Kutub), 1890.
- Zazzo JF, Rouveix B, Rajagopalan P, et al. Effect of zinc on the immune status of zinc-depleted AIDS related complex patients. *Clin Nutr*. 1989;8(5):259-261.