Original Article

Tracing The Voyage of Black Seed (*Nigella Sativa*): From Ancient Applications To Modern Age Research

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Abstract

The history of black seed (Nigella sativa) traces back to the origins of human civilisation. Its earliest presence was reported in a small flask used by the Hittites (1650 BC) for carrying medicines, found in an ancient monument in Anatolia (modern-day Turkey). Another notable reference is its finding in the tomb of Tutankhamun (1341–1323 BC), the Egyptian pharaoh, where it was believed to be a remedy for seizures in the afterlife, as he likely suffered from epilepsy or cerebral malaria. The earliest written evidence appears in the Book of Isaiah from the Old Testament (8th century BC). Greek and Roman physicians, including Hippocrates, Dioscorides, and Galen (460 BC to 216 AD), referred to black seed as "Melanthion", meaning "tiny black seed", and prescribed it as a remedy for various ailments. Black seed also holds a significant place in ancient Arabic, Ayurvedic, and Chinese Traditional medicine. A notable Islamic reference is the Hadith of Prophet Muhammad (Peace and blessings be upon him) (571–632 AD), who said, "Use the black seed, for it is a cure for all ailments except death" (Al-Bukhari). During the Middle Ages, Islamic physicians, particularly Ibn Sina (980–1037 AD), extensively documented its therapeutic applications in the "Canon of Medicine", including its use as a treatment for cancer. In the modern era, black seed has gained scientific recognition for its diverse pharmacological properties, which are attributed to its rich composition of medicinal compounds. This article chronicles the historical significance of black seed and bridges its traditional uses with contemporary scientific discoveries, underscoring its enduring role in human health.

Keywords: Black seed, history, folk medicine uses, pharmacological properties, present-day studies, confirming validity of ancient uses.

Introduction

In recent years, interest in Complementary and Alternative Medicine (CAM) has grown significantly, especially as a potential remedy for ailments where conventional medical treatments often fall short. Disillusioned by the limitations of modern medicine, many individuals are turning back to traditional systems of healthcare, such as Chinese Acupuncture, Ayurvedic Medicine from India, and Arabic-Islamic Traditional Medicine. Among the many therapeutic herbs utilized in these ancient practices, *Nigella sativa* (*N. sativa*) stands out as a key remedy for numerous diseases, with its use prominently documented in Chinese, Ayurvedic, Arabic, and other historical medical traditions [1-3]. *N. sativa* belongs to the Ranunculaceae family of plants and is predominantly cultivated in regions such as Central Asia, the Middle East, North Africa, and the Indian Subcontinent. The plant grows to a modest height of 2–3 feet, with slender, pointed leaves and delicate flowers in shades of whitish-purple or yellow. Upon ripening, the fruit encases tiny black seeds, which have been the focus of its medicinal value (Figure 1) [4]. Known by various names across cultures, *N. sativa* is commonly referred to in English as "Black Seed", in Arabic as "Al-Habba Al-Saudah", in Urdu as "Kalonji", in Turkish as "Çörek Otu", in Persian as "Siyah Daneh", in Hebrew as "Ketzah", in Greek as "Melanthion", in Spanish as "Niguilla", in Swedish as "Svartkummin", in Italian as Nigella), Russian as "Chernushka", in Thai "Thian dam", in Chinese as "Hei Zhong Cao", and in Japanese as "Nigera" [5]. This diverse nomenclature reflects the widespread recognition of the plant and its profound significance in traditional medicine worldwide.

Figure 1: *Nigella sativa* plant with flowers and fruits (Shuttle stock images) [4].

The extensive application of *N. sativa* in traditional medicine has spurred considerable interest in scientific research aimed at uncovering its medicinal properties and bioactive constituents. A simple search on PubMed revealed over 500 publications dedicated to *N. sativa*. This herb is now recognised as a promising source for developing novel therapies for a variety of challenging diseases, including cancer, diabetes, asthma, hypertension, and infectious diseases caused by bacteria, fungi, and viruses [6, 7, 8]. Historical accounts trace the use of black seeds as far back as 3670 BC, with references to their name and medicinal uses found in religious texts and the writings of renowned physicians from antiquity and the Middle Ages. The geographical awareness of its therapeutic applications spans centuries, underscoring its enduring importance.

Numerous reviews have briefly addressed the historical significance of *N. sativa* and its documented medicinal properties [4, 9, 10]. Given the broad geographic spread and multifaceted medicinal applications of *N. sativa*, a more detailed exploration of its historical significance is essential. This work provides an in-depth account of the key historical milestones associated with this remarkable herb while correlating its traditional uses with findings from contemporary scientific studies. By shedding light on both its ancient heritage and modern relevance, this effort aims to enhance the general awareness of the potential of *N. sativa* as a natural remedy. Furthermore, it aims to inspire researchers to conduct further studies exploring its therapeutic properties, clinical applications, and the synthesis of innovative medicinal compounds derived from its active ingredients.

Materials And Methods

The present manuscript is the result of an extensive online exploration of research papers and reputable websites dedicated to the history and medicinal significance of black seed (*N. sativa*). The historical aspects of black seed are divided into: mention of black seed in religious books, presence in ancient Hittite and Egyptian monuments, Prescription by Ancient Greek and Roman Physicians, Use in Ayurvedic and Chinese Medicine, and Application in Arabic/Islamic Medicine in the Middle Ages. At the end of each section, some of the scientific research conducted in the modern era, relevant to the prescription of black seeds in the ancient systems of medicine, is also narrated.

Mention of Black Seed in Religious Books

a. Book of Isaiah (Peace be upon him):

Isaiah ben Amoz (peace be upon him), a prophet of the 8th century BC, is revered and honoured equally by Jews, Christians, and Muslims. His prophetic role is detailed in works such as *Isaiah among the Ancient Near Eastern Prophets* by Matthijs J. De Jong and *History of Prophets* by Ibn Kathir [11-15]. The writings of Isaiah (peace be upon him) are believed to have been revealed alongside the Dead Sea Scrolls, which predate the time of Jesus by approximately a century (Figure 2) [16, 17]. This ancient script offers a profound historical connection to *Nigella sativa*, underscoring its long-standing significance in traditional medicine and spiritual practices.

(a) (b)

Figure. 2. (a). A fragment of the Book of Isaiah (Peace be upon him) found among the Dead Sea Scrolls. (b). Scroll of the Book of Isaiah (Peace be upon him), Hebrew Bible manuscripts [17].

In the *Book of Isaiah*, part of the Old Testament, Isaiah (Peace be upon him) refers to *Nigella sativa* (*N. saiva*) as "Ketzah", marking it as one of the earliest written mentions of the herb. The Hebrew word *Ketzah* in the *Book of Isaiah* refers to the black seed (*N. sativa*). However, its translation varies across the different versions of the Bible. In the King James Version (KJV), it is rendered as "Fitches", in the Revised Standard Version (RSV) as "Dill", and in the New World Translation (NWT) as "Black Cumin". Notably, James A. Duke, in *Duke's Handbook of Medicinal Plants of the Bible,* supports the NWT translation, identifying *N. sativa* as "Black Cumin" [18].

In the New King James Version (NKJV), *N. sativa* is also translated as "Black Cumin" and is mentioned in Isaiah 28:25–27 [19] as follows:

25: "When he has leveled its surface, does he not sow the black cumin, and scatter the cumin, plant the wheat in rows, the barley in the appointed place, and the spelt in its place?"

26: "For He instructs him in right judgment, His God teaches him".

27: "For the black cumin is not threshed with a threshing sledge, nor is a cartwheel rolled over the cumin, but the black cumin is beaten out with a stick".

One may wonder why *N. sativa* is particularly mentioned in the Book of Prophet Isaiah (Peace be upon him) and stated along with wheat. The following are some suggestions for this context. First, many medicinal plants, such as flex or linseed (*Linum usitatissmum*), fennel seed (*Foeniculum vulgare*), poppy seed (*Papaver somniferum*), and black cumin, were cultivated along with wheat. They were mostly sown as a scatter, while the wheat was planted in rows (Versus 28:25). Second, man does all this according to the wisdom given by God Almighty (Verse 28:26). Third, black cumin plants are harvested and threshed separately from wheat, simply by beating with a stick, because of the small size and fine texture of its plant and seeds (Versus 28:27). Finally, wheat is a major food grain, and black cumin is cited along with wheat, perhaps to emphasise its use as a main remedy for many ailments.

b. Narrations of Prophet Mohammad (Peace and blessings be upon him):

The medicinal value of *N. sativa* (black seed) is emphasised in authentic Islamic traditions, specifically in the *Hadiths* of the Prophet Muhammad (peace and blessings be upon him). These narrations, found in the respected collections of *Sahih Al-Bukhari* and *Sahih Muslim,* highlight the extraordinary therapeutic properties of the black seed.

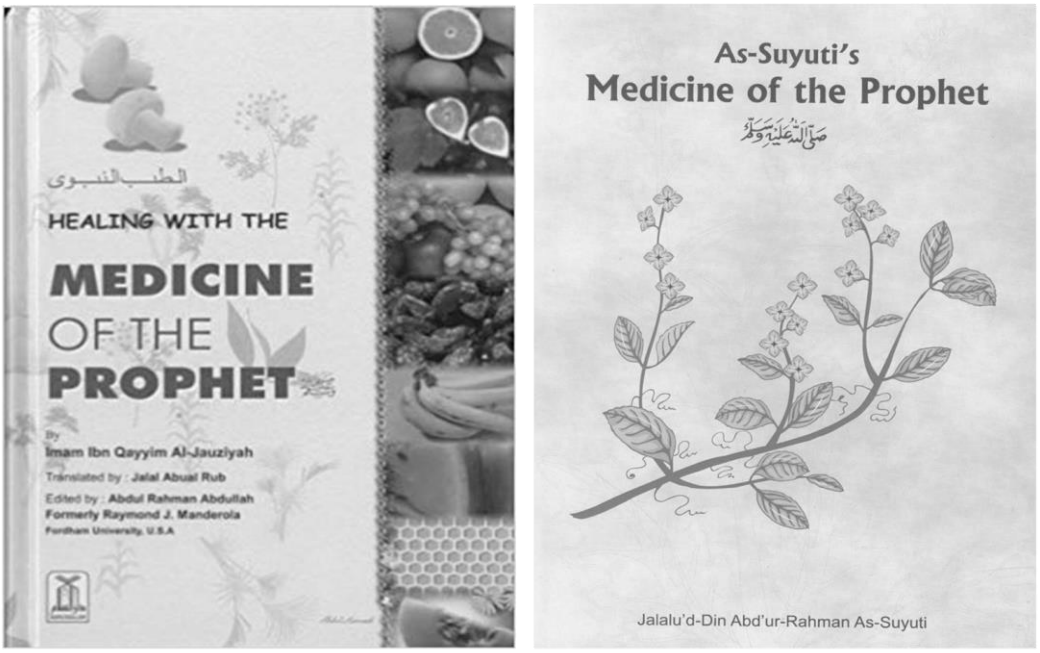
In a narration from *Sahih Al-Bukhari*, Aisha (May Allah be pleased with her) reported that the Prophet Muhammad (Peace and blessings be upon him) said, "This black seed is a cure for all ailments, excluding 'As-Sam'. "When Aisha inquired about the meaning of 'As-Sam,' the Prophet (Peace and blessings be upon him) clarified: "Death" [20].

Similarly, Abu Hurairah (May Allah be pleased with him) narrated another *Hadith*, recorded in both *Sahih Al-Bukhari* and *Sahih Muslim*, in which Allah's Messenger (peace and blessings be upon him) said, "Black cumin is the cure for all ailments, other than death" [21, 22].

N. sativa is also extensively discussed in the compendium *Al-Tibb Al-Nabawi* (The Medicine of the Prophet), composed by Imam Shams al-Dīn Abū-Abd-Allāh, commonly known as Imam Ibn Qayyim al-Jawziyyah (1292–1350 CE) [23]. This inspiring work lists numerous medicinal applications of black seed and its oil, including:

- It relieves flatulence, dyspepsia, and haemorrhoids and expels intestinal worms.
- It is useful in the treatment of the common cold, sneezing, and fever.
- It relieves toothache, headache, and facial paralysis.
- Effective in the management of dropsy, dyspnoea, and other asthmatic symptoms.
- Alleviation of renal stones, improvement of menstrual flow, and enhancement of milk production in lactating mothers have been reported.
- Healing of skin ulcers, wounds, soft and hard tumours, and insect bites, including snake and rabid dog bites.
- Burning black seeds to produce smoke repels or kills insects.

Imam Jalal-al-Din Abdul-Rehamn As-Suyuti (1445–1505 CE), another esteemed Islamic scholar, echoed these benefits in his work, *As-Suyuti's Medicine of the Prophet* [24]. He briefly reiterated many of the therapeutic uses of black cumin, aligning with those described by Ibn Qayyim al-Jawziyyah. **Figures 3a and 3b** illustrate excerpts and manuscripts from these iconic Islamic medical texts, underscoring the remarkable legacy and medicinal significance of *N. sativa*.



(a) (b)

Figure 3: Title pages of the English translation: (a) 'Al-Tib Al-Nabavi', Healing with the Medicine of the Prophet' (Peace and blessings be upon him), by Imam Ibn Qayyim Al-Jawziyah [23]. (b) As-Suyut's Medicine of the Prophet (peace and blessings be upon him) [24].

Present-day research relevant to the uses of black seed in 'Medicine of the Prophet Mohammad' (Peace and blessings be upon him):

The medicinal properties of *N. sativa* extend significantly to the gastrointestinal system and liver, showing its broad therapeutic potential in both traditional and modern medicine settings. Oral administration of *N. sativa* powder effectively alleviated flatulence [25]. *N. sativa* oil reduced gastric mucosal histamine levels and prevented ethanol-induced ulcers in rats, highlighting its protective role against gastric injuries [26]. Black seed powder successfully eradicated *Helicobacter pylori* in patients with non-ulcer dyspepsia, demonstrating efficacy comparable to that of standard triple therapy regimens [27]. Thymoquinone (TQ), an active compound in *N. sativa*, exhibits potent activity against anaerobic bacteria, such as *Clostridium difficile,* a common cause of diarrhoea associated with broad-spectrum antibiotic use and proton pump inhibitors [28]. *N. sativa* seeds and their ethanolic extracts effectively reduced faecal egg counts of cestodes in children, achieving results similar to the antiparasitic drug niclosamide [29]. Additionally, *N. sativa* seed and menthol extracts expelled rumen flukes (*Paramphistomum*) from the intestines,

with efficacy comparable to netobimin, an anthelmintic agent [30]. TQ protects against liver damage and the toxic effects of sodium fluoride in rats by reducing oxidative stress and preventing toxin accumulation [31]. The antioxidant, anti-inflammatory, and anti-fibrotic effects of *N. sativa* provide hepatoprotective effects against various liver injuries and diseases and hinder the accumulation of scar tissue characteristics of liver fibrosis [32]. In a comprehensive review, the various effects of N. sativa on the gastrointestinal tract, including the liver and pancreas, have been adequately summarised [33].

Nigellon, an active compound in *N. sativa*, effectively alleviates asthma and bronchitis symptoms, especially in children [34, 35]. Extracts of *N. sativa* prevented guinea pig tracheal constrictions induced by carbachol and histamine, showcasing its bronchodilatory effects [36]. Black seed extracts demonstrated smooth muscle relaxation in rabbit tracheal and jejunal tissues [37]. Topical application of *N. sativa* oil completely relieved mild nasal allergy symptoms and significantly improved moderate to severe cases [38]. TQ reduces interleukin-4 (IL-4), immunoglobulin E (IgE), tumour necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) levels in allergic rhinitis, demonstrating its anti-inflammatory mechanism [39]. The essential oil of black seed decreased white cell counts in guinea pig bronchial secretions, confirming its anti-inflammatory effects in respiratory conditions [40]. TQ showed antituberculous activity in vitro by inhibiting *Mycobacterium* growth in Middlebrook agar and broth, with a minimum inhibitory concentration (MIC) of 20 µg/mL [41]. Recently, a review article summarised the therapeutic potential of *N. sativa* against various respiratory problems, including asthma, dyspnoea, nasal dryness, and rhinitis. [42]. These findings align with the respiratory uses of black seeds described in *Al-Tib Al-Nabavi*.

Topical *N. sativa* extract treatment of local *Staphylococcus* infections reduced leukocyte counts in the affected areas [43]. Black seed extracts delayed papilloma formation and significantly reduced tumour counts in a mouse skin cancer model induced by croton oil. Intraperitoneal administration controlled the growth of soft-tissue sarcomas in albino mice [44]. Aljabre and colleagues compiled the dermatological uses of black seed, including its efficacy against infections, ulcers, wounds, and tumours [45]. Moreover, Abbas et al. have extensively reviewed the antimicrobial activities of *N. sativa* [46]. These results corroborate the use of black seeds in skin conditions, as described in *Al-Tib Al-Nabavi*. These studies are linked to the use of Black Seed for skin infections, ulcers, wounds, and hard and soft tumours mentioned in 'Al-Tib Al-Nabavi' (Peace and blessings be upon him).

Headache, toothache, joint pain, body aches, and fever are commonly encountered symptoms, and the black seed has been recommended for their relief in 'Al-Tib Al-Nabavi' (Peace and blessings be upon him). Presently, there are a large number of studies reported in the literature on the effectiveness of black seeds and their constituents in these conditions. Black seed polyphenols relieve pain and inflammation. Pain control was assessed in mice and rats by controlling writhing induced by acetic acid and formalin. Control of inflammation was tested by preventing hind paw oedema produced by carrageenan and ear oedema by croton oil [47].

More recently, in addition to the assessment of pain and inflammation relief by the techniques mentioned above, the investigators elucidated the possible mechanism of action of phenols and polyphenols of black cumin, such as ferulic acid, p-coumaric acid, kaempferol, and quercetin. Ferulic acid inhibits the synthesis of phospholipids essential for the formation of arachidonic acid, which is a precursor of inflammatory mediators (prostaglandins and leukotrienes). Quercetin, p-coumaric acid, and kaempferol decreased the formation of pro-inflammatory proteins (myc, MAPK, EGFR, and TNF), which increased the production of arachidonic acid, thus reducing arachidonic acid and ultimately prostaglandin and leukotriene formation. Moreover, these components of black seed directly reduce the activity of cyclooxygenase-1 and cyclooxygenase-2, enzymes required for the synthesis of prostaglandins [48]. The analgesic and anti-inflammatory properties of *N. sativa* stem from its ability to inhibit inflammatory mediator precursors and suppress the enzymes involved in their synthesis.

These findings not only validate the traditional uses of BSE but also provide a scientific basis for its therapeutic potential of black seed in managing pain and inflammation.

Black Seeds in Ancient Egyptians and Hittites Monuments

a. Ancient Egyptians

Ancient Egyptian history records that, alongside numerous household and personal items, seeds, fruits, and leaves, *N. sativa* seeds were also uncovered in the tomb of King Tut [4, 49]. The presence of black seed among the burial goods may reveal that in those days, black seed was considered an important remedy for many ailments, including epilepsy and malaria. From the suggestions regarding the cause of King 'Tut's death, it can be anticipated that he was advised to use the black seed as a remedy for his ailments when he was alive and then kept it in his tomb for use in the next life, as they believed. Interestingly, recent research has verified the effective role of black seeds in seizures and cerebral malaria (mentioned at the end of this section).

Ancient Egyptian queens, such as Nefertiti and Cleopatra VII, have been stated to use black seed and its oil for augmentation of their natural beauty and health. Black seed oil possesses unique properties, such as moisturization, emollience, frivolous touch, and rapid absorption without blocking skin pores. Its consistent application gives a

glowing appearance and enhances natural beauty. Thus, making black seed oil an optimal choice for skin care in the hot and dry weather of Egypt since ancient times [50]. Because of their widespread use for many ailments, Black Cumin seeds were called a panacea in ancient Egypt, meaning the cure for all diseases and evils. The name '**Panacea'** was given, perhaps, after the Greek goddess of universal remedy, 'Panakeia' [51].

Scientific studies linked to the use of *N. sativa* in epilepsy, malaria & skincare

N. sativa oil, when administered before pentylenetetrazol (PTZ), a convulsant drug, prevented fits in mice more effectively than Na Valproate [52]. Thymoquinone (TQ), an active component of black seed, reduced seizures induced by PTZ in mice and prevented death in mice given maximal electroshock therapy [53]. *N. sativa* water extract for 4 weeks as an adjunct therapy significantly decreased the frequency of seizures in children with refractory seizures compared to placebo [54].

N. sativa seed extract showed 100% inhibition of *Plasmodium falciparum* schizont maturation [55]. Methanolic extracts of black seeds treated malaria and reduced oxidative stress in a *Plasmodium yoelli nigeriensis* infection model in mice [56]. Similarly, the water, ethanol, and chloroform extracts of black seed treated malaria and controlled oxidative stress in the *Plasmodium berghei* infection model in mice [57-59].

Black seed oil has been shown to reduce skin irritation and dryness [60]. N. sativa hydrogel significantly reduced comedones, papules, and pustules of acne in the treatment group compared to the placebo [61]. As mentioned earlier, Salih Aljabre et al. reviewed various dermatological effects of black seed, such as anti-bacterial, anti-fungal, anti-viral, anti-eczema, and anti-psoriasis effects [45].

b. Ancient Hittites

The Hittites were residents of ancient Anatolia (currently in Turkey) and built a strong empire between 1600 and 1180 BC [62]. They used to travel from Anatolia to Palestine, the Holy Land, where important shrines were located, and a range of pilgrim ephemera was produced there, including pilgrim flasks. These pilgrim flasks were used to carry food, water, scents, and medicaments. These flasks were made of pottery in ancient times and later, during the Roman Empire, were prepared from metal, glass, or porcelain, and have been found in monuments of the Mediterranean region and beyond [63].

Recently, some pilgrim flasks discovered in monuments in Anatolia were found to contain black seeds. Archaeologists have linked these flasks to the Old Hittite Period, around 1650 BC. Since ancient times, black seeds in combination with honey have been extensively used for the management of many ailments in Middle Asia, the Middle East, and Southeast Asia. The beneficial role of black seeds has been confirmed in several scientific studies [64].

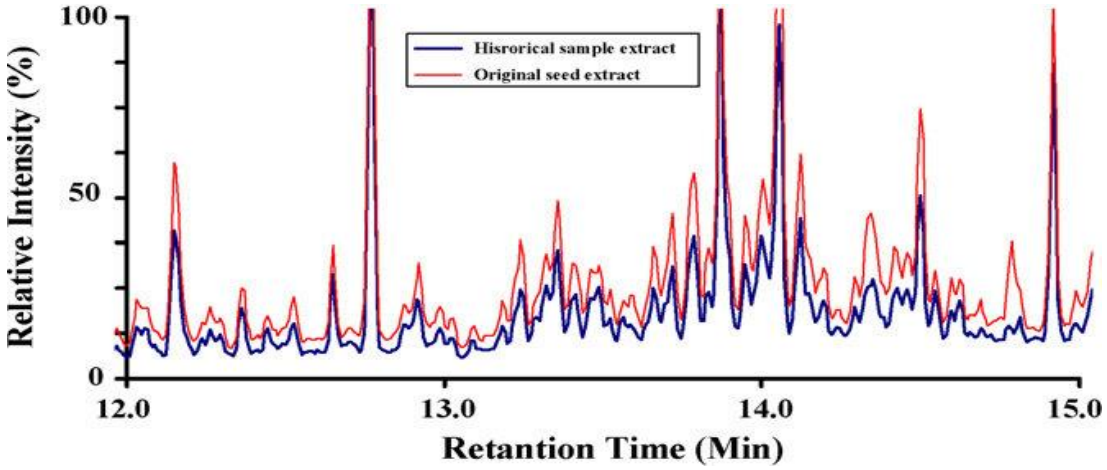


Figure 4. GC–MS chromatograms of sample extracts in ethanol. Extract of historical Nigella seeds from pilgrim flask (blue). Extraction of present-day seeds (Red) [64].

Similarities between ancient nigella seeds and present-day seeds.

Black seeds recovered from a pilgrim flask found in monuments of Anatolia linked to the Old Hittite Period were comparable to present-day black seeds in terms of their appearance and chemical constituents. Chromatographic-mass spectrometric (GC-MS) analysis of the ethanol and dichloromethane extracts of ancient and modern seeds revealed similar essential oil contents (Figure 4) [64].

Black Seed and Ancient Greek and Roman Physicians

Hippocratus of Kos, Hippocrates II (460-370 BC)

Hippocrates II was a well-known physician in Classical Greece. His contributions revolutionised clinical practice and he is generally known as the “Father of Medicine” (Figure 5a) [65]. The English translation of Hippocrates' work related to medicine is available in XI volumes and provides basic knowledge of ancient Greek medicine. The eleventh volume of his work contains valuable knowledge about the female reproductive system, diseases of the female reproductive organs, and treatment of women's illnesses. (Figure 5b) [66].
Ethiopian Black Cumin (*N. sativa*) is included in the recipients aimed at the treatment of diseases of women and children given in volume XI of the ‘Hippocrates' Book of Greek Medicine, mentioned above. For example, a recipe for swelling (Inflammation) of the womb in women (vaginal thrush) and oral cavity (oral thrush) in infants and cough in children comprises black seeds, flaxseeds, paeony roots, and Vinca minor stems [67].

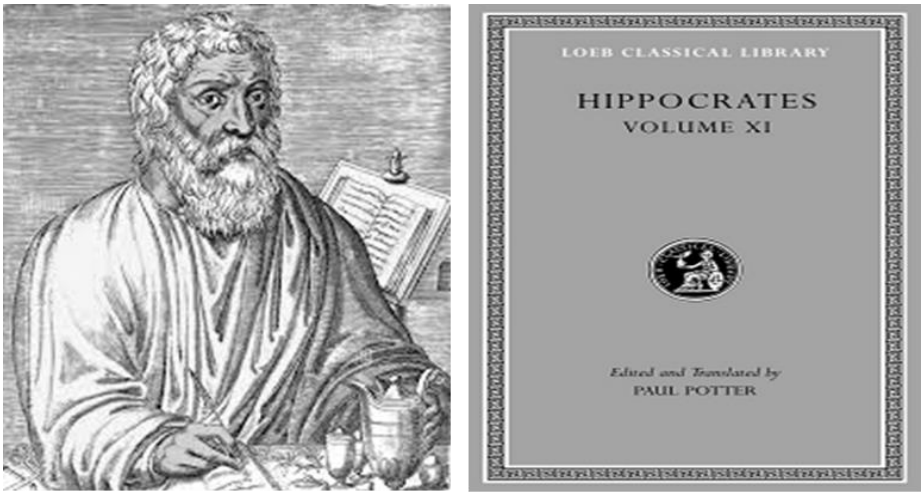


Figure 5. (a) Presentation of Hippocrates (b) Cover page of volume XI of Hippocrates Book of Greek Medicine, which contains a description of the women’s reproductive system, its diseases, and their treatment [65]

Pedanius Dioscorides (90-40 AD) was another great physician of ancient Greece, born in Anazarbos (Now Nazarba, in Turkey) (Figure 6a). He was an eminent army physician who served under the Roman Empire in Greece, Italy, Asia Minor, and France. During his military service, he had the opportunity to acquire knowledge about medicinal herbs from different regions. Dioscorides compiled his famous book, De Materia Medica, ' in five volumes, which remained the reference book for Greek and Roman herbal medicines (Figure 6b). Medicinal properties of *N. sativa*, including treatment of psoriasis and for removing rough skin from the face, are mentioned in volume-1 of 'De Materia Medica' and is named 'Melanthelaion' (or ‘Melanthion') in Greek, which means ‘tiny black seed’ [68].

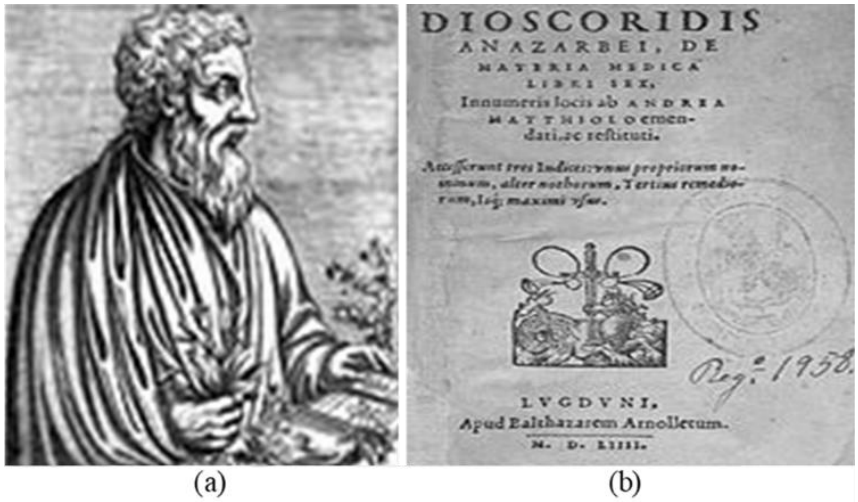
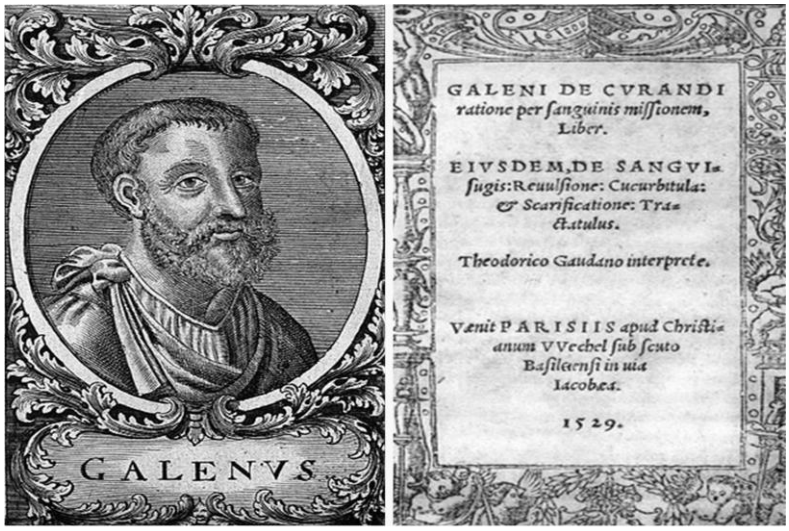


Figure 6. (a) Presentation of Dioscorides (b) Cover page of an ancient form of De Materia Medica, Lyon, France, 1554 [69, 70].

Galenus, 129-200/216 AD (Figure 7a) was also a famous physician of the Roman Empire who was born in Pergamon (Present-day Bergama, in Turkey). He was the personal physician for Roman Emperors of his time and introduced new medical theories and discoveries [71].



(a) (b)

Figure 7. (a). Depiction of Galenus, commonly known as Galen. (b). Front page of his famous book, 'Galeni de Cvrandi' (meaning, 'Simple Drugs by Galen') [72].

The standard terms used to designate the common cold' in the Greek language were '*koruza'* and '*'katarrhos,* (hence the modern-day terms 'coryza' and 'catarrh'). Galen proposed that such ailments are caused by wet and cold humour and, therefore, must be treated with hot and dry medicines, such as Melanthion', or black seed, mentioned in Volume 7 of his classic book, 'Galen On Simple Drugs' (Figure 7b) [72, 73].

Surprisingly, in the present-day modern era, Moroccans apply tiny black seeds for the management of flu and stuffy noses using a method similar to that prescribed by Galen about 2000 years ago. A teaspoon of Nigella seeds is wrapped in a small piece of linen and rubbed briefly in the hand to warm it up a bit. The tiny parcel of black seed is brought close to one nostril while the other is blocked with the thumb, and fumes are then deeply inhaled. The procedure is repeated as often as necessary until the nose is unblocked [73].

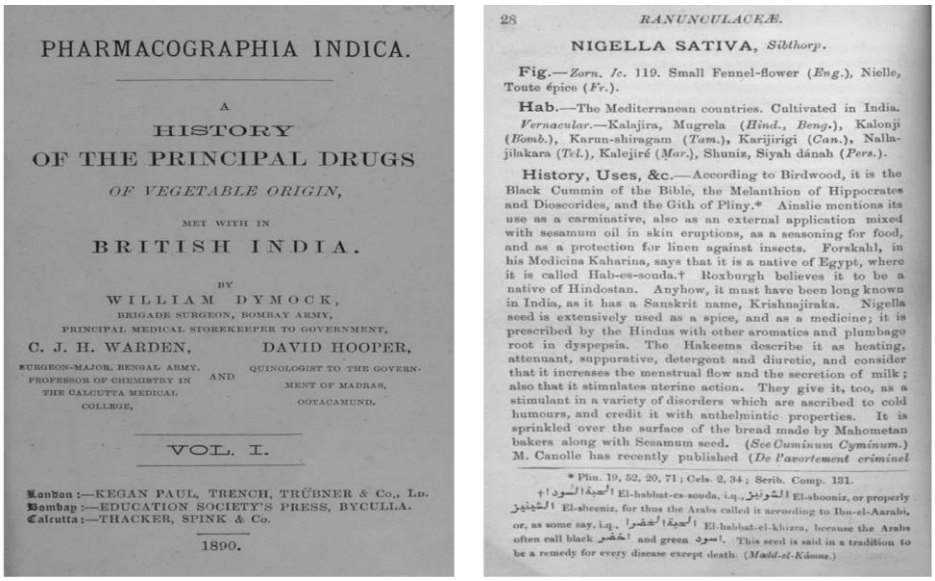
Studies related to Black Seed use by ancient Greek and Roman physicians for oral & vaginal thrush, psoriasis, rough skin, common cold, and spring catarrh:

In *in vitro* experiments, the black seed ether extract suppressed the growth of *Candida albicans,* [74]. Similarly, in *in vivo* experimental models, black seed extract inhibited the multiplication of *Candida* yeasts in many tissues [75]. Thymoquinone, thymohydroquinone, and thymol, the active components of *N. sativa*, inhibited clinical isolates of Candida moulds and yeasts, as well as many species of dermatophytes [76]. Nanoparticle thymoquinone inhibited *Candida albicans* yeasts and *Candida* biofilms more effectively than its non-nano counterpart [77]. Black seed extract in ethanol was shown to suppress psoriatic lesions in mouse tail models. The extract produced significant epidermal differentiation, $71.36 \pm 2.64\%$, compared to negative controls, $17.30 \pm 4.09\%$ [78]. Recently, the therapeutic potential and molecular mechanisms of *N. sativa* in chronic inflammatory diseases have been reviewed by Rashwan et al. [79]. The anti-aging, moisturising, mitigating, and protective effects of black seed oil were mentioned in the section on the use of *N. sativa* by ancient Egyptian queens.

The beneficial effects of black seed in flu and spring catarrh are probably related to the inhibitory action of nigellone on histamine release from mast cells, as demonstrated by Chakarvarti in 1993 [80]. Black seed oil and thymoquinone inhibit cyclooxygenase and lipoxygenase enzymes, leading to a decrease in the formation of inflammatory mediators from arachidonic acid, such as prostaglandins and leukotrienes [81]. The results of a randomised, double-blind, placebo-controlled study conducted to evaluate the effect of N. sativa oral (NSO) capsules for the relief of upper respiratory symptoms such as sneezing, rhinorrhoea, nasal obstruction, and itching demonstrated a significant decrease in the total nasal symptom score and total ocular symptom score in the NSO group compared to placebo. Serum Immunoglobulin E levels also decreased in the NSO group [82].

Ayurvedic Medicine and Black Seed

N. sativa and its oil have been commonly used in Ayurvedic Medicine since ancient times in the Indian subcontinent. A brief note on its history, uses, and names in local languages is given in the Pharmacographia Indica by William Dymock (1890), which includes a description of herbal drugs in British India (Figure 8) [83]. It is also mentioned in the Ayurveda Pharmacopoeia of India, published by the Government of India under the name Upakunchika [84].



PHARMACOGRAPHIA INDICA.

A
HISTORY
OF THE PRINCIPAL DRUGS
OF VEGETABLE ORIGIN,
MET WITH IN
BRITISH INDIA.

BY
WILLIAM DYMOCK,
BRIGADE SURGEON, BOMBAY ARMY,
PRINCIPAL MEDICAL STOREKEEPER TO GOVERNMENT,
C. J. H. WARDEN, SURGEON-MAJOR, BENGAL ARMY, PROFESSOR OF CHEMISTRY IN THE CALCUTTA MEDICAL COLLEGE,
AND
DAVID HOOPER, QUINOLOGIST TO THE GOVERNMENT OF MADRAS, OOTACAMUND.

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Calcutta:—THACKER, SPINK & Co.

1890.

(a)

28 *RANUNCULACEÆ.*

NIGELLA SATIVA, *Sibthorp.*

Fig.—*Zorn. Ic.* 119. Small Fennel-flower (*Eng.*), Nielle, Toute épice (*Fr.*).

Hab.—The Mediterranean countries. Cultivated in India.

Vernacular.—Kalajira, Mugrela (*Hind., Beng.*), Kalonji (*Bomb.*), Karun-shiragam (*Tam.*), Karijirigi (*Can.*), Nallajilakara (*Tel.*), Kalejiré (*Mar.*), Shuniz, Siyah dánah (*Pers.*).

History, Uses, &c.—According to Birdwood, it is the Black Cummin of the Bible, the Melanthion of Hippocrates and Dioscorides, and the Gith of Pliny.* Ainslie mentions its use as a carminative, also as an external application mixed with sesamum oil in skin eruptions, as a seasoning for food, and as a protection for linen against insects. Forskahl, in his Medicina Kaharina, says that it is a native of Egypt, where it is called Hab-es-souda.† Roxburgh believes it to be a native of Hindostan. Anyhow, it must have been long known in India, as it has a Sanskrit name, Krishnajiraka. Nigella seed is extensively used as a spice, and as a medicine; it is prescribed by the Hindus with other aromatics and plumbago root in dyspepsia. The Hakeems describe it as heating, attenuant, suppurative, detergent and diuretic, and consider that it increases the menstrual flow and the secretion of milk; also that it stimulates uterine action. They give it, too, as a stimulant in a variety of disorders which are ascribed to cold humours, and credit it with anthelmintic properties. It is sprinkled over the surface of the bread made by Mahometan bakers along with Sesamum seed. (*See Cuminum Cyminum.*) M. Canolle has recently published (*De l'avortement criminel*

* Plin. 19, 52, 20, 71; Cels. 2, 34; Scrib. Comp. 131.

† الحبة السوداء El-habbat-es-souda, i.q. الشونيز El-shooniz, or properly الشنيز El-sheeniz, for thus the Arabs called it according to Ibn-el-Aarabi, or, as some say, i.q. الحبة الخضرا El-habbat-el-khizra, because the Arabs often call black اخضر and green اسود. This seed is said in a tradition to be a remedy for every disease except death. (*Madd-el-Kámus.*)

(b)

Figure 8. (a). Title page of Pharmacographia Indica by William Dymock (1890). (b). Description of *N. sativa* on its page 28 [83].

The description of the domestic and clinical applications of black seed and its oil mentioned in these books is not much different from those given in books of traditional Greek and Arabic Medicine, for example, 'Galen on Simple Drugs' and 'Kanoon Fi-Altib', by Ibne-Sina (Described in the section on the 'Use of Black Seed in Greek and Arabic Herbal Medicine'). Perhaps, because of the invasion of Muslim Emperors and the travel of many scholars of herbal medicine from Middle Asia to the Indian Sub-continent in the Middle Ages. The common name used for the system of herbal medicine in the Indian subcontinent is 'Unani Tib', meaning 'Greek Medicine'.

Uses of Kalonji Powder in Ayurveda:

The following is a summary of the main uses of Black Seed in Ayurvedic medicine [84]:
Rochanam & Pachanam: Important spice that supports digestion.
Deepanam: means to ignite, thus stimulating appetite and boosting metabolism.
Dadurgandhya nashanam: Alleviates bad breath.
Samgrahi: Relieves diarrhoea, dysentery, and assimilatory disorders.
Chhardi atisarhrit: *N. sativa* powder is useful for vomiting and diarrhoea.
Sandhanayogya: Promotes healing of wounds and helps in the union of bone fractures.
Pravarttyarttavam: Induces healthy menstrual cycle. It cleanses the uterus after delivery.
Vrishyam: improves fertility.
Medhyam: Means a supplement that supports the nervous system.
Jwarghnam Balyam: Relieves fever and improves physical and psychological discomfort.
Chakshushyam: *N. sativa* powder nourishes the eyes and improves vision.

Studies corresponding to the use of Black Seed in Ayurvedic medicine:

Most of the studies relevant to the use of *N. sativa* in Ayurveda are given above in various sections, for example, related to effects on the gastrointestinal tract, analgesic-antipyretic actions, wound healing, and control of infections. Some recent studies related to its use in neurological and gynaecological disorders and male fertility are summarised below:

In addition to peripheral analgesic and anti-inflammatory effects, *N. sativa* and its active components have been shown to possess anti-nociceptive actions on the central nervous system in experimental animals. In the pain control areas of the central nervous system, *N. sativa* and its components activate μ- and κ- opioid receptors [85]. The extracts of *N. sativa* and its active components effectively controlled the depressive features produced by lipopolysaccharides in rats [86]. Black seed, given as a nutritional supplement, has been shown to have a positive effect on mood and anxiety [87]. The methanolic extract of black seeds increased the output of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and lowered the release of excitatory transmitters (glutamic acid, aspartic acid, and glycine) in neuron cell cultures, suggesting the relevance of these findings to sedative-antianxiety action [88].

Thymoquinone improved the behaviour and biochemical profiles of Parkinson's disease rat models [89]. Another study revealed that black seed given for a longer period in rats elevated brain 5-HT levels and enhanced their capacity to learn and remember [90]. In a clinical study on normal healthy elderly participants aimed to study black seed actions on recall, awareness, and intellect demonstrated noteworthy improvement as compared to placebo. The tests performed to test memory and intellectual functions included logical memory Test-I and II, total score of digit span, 30 min delayed-recall, percent score in Rey-Osterrieth figure, time taken to complete letter cancellation, and time taken in trail making [91]. The results of these studies show that black seed may be recommended as a nutritional additive for the control of Parkinsonism and Alzheimer's disease in elderly persons.

Black seed volatile oil inhibited spontaneous uterine smooth muscle contractions in virgin guinea pigs and rats, as well as contractions induced by oxytocin [92]. Black seed fixed oil blocked oxytocin and prostaglandin E2-induced uterine contractions in pregnant rats [93].

Studies aimed to determine the benefit of oral black seed, and its extracts and active component (Thymoquinone and linoleic acid) administered via intra-gastric gavage in ovariectomized rats revealed significant improvement in symptoms of menopause, serum oestrogen, and histological changes of uterus and vaginal epithelium [94]. *N. sativa* seed extract was shown to possess strong oestrogenic and LH-like activities, and to increase serum levels of LH P4 hormone. Moreover, it demonstrated interaction with Erβ, LH, and GnRH, and P4 receptors, suggesting its potential for enhancing female fertility [95]. Besides animal experiments many human studies have also been reported to demonstrate beneficial effects of N. sativa on female reproductive system. The results of a systemic review to find effects of *N. sativa* on female infertility revealed that *N. sativa* and its active component, Thymoquinone, could reduce Malondialdehyde (MDA) levels, and increase Superoxide Dismutase (SOD), Total Antioxidant Status (TAS), and the number of ovarian follicles, thus improve fertility in women [96]. More recently, N. sativa was also shown recover ovarian dysfunctions in Polycystic Ovary Syndrome [97]. Oral *N. sativa* seed with topical N. sativa oil relieved symptoms of Female Sex Disorder in peri- and post-menopausal, such as dryness of vagina, dyspareunia, and decreased desire, orgasm and satisfaction; due to their systemic and topical oestrogenic, anti-inflammatory and analgesic potential, besides lubrication [98]. These findings propose the possible use of black seed oil in uterine disorders, such as dysmenorrhoea, habitual abortion, premature delivery, as well as female infertility and menopausal disorders.

The benefits of black seed extract on the male reproductive system of rats and mice have also been determined by some investigators, who reported an increased thickness of the germinal layer and a decrease in the epithelial layer of the seminiferous tubules. The seminal vesicle size and weight were also increased. Moreover, there was a substantial increase in the number of spermatogonia, spermatocytes, spermatids, spermatozoa, Sertoli cells, Leydig cells, testosterone, and follicle-stimulating hormone levels [99-101]. In a clinical study, the administration of *N. sativa* for 3 months significantly increased sperm count, motility, viability, and semen volume. Serum FSH, LH, and testosterone levels were also significantly increased after 3 months of treatment with N. sativa [102]. A recent study on human spermatozoa reported that *N. sativa* extract protected sperm against oxidative stress, reduced ROS production, improved sperm parameters, such as motility, plasma membrane function, and mitochondrial membrane potential, and prevented DNA damage [103].

N. sativa in Traditional Chinese Medicine (TCM)

Names of black seed in Chinese Language [98]:

Ancient Chinese Medicine, Hei ku ming

Name in Traditional Chinese Medicine: 黑种草子 (Hei Zhong Cao)

Uses of *N. sativa* in TCM

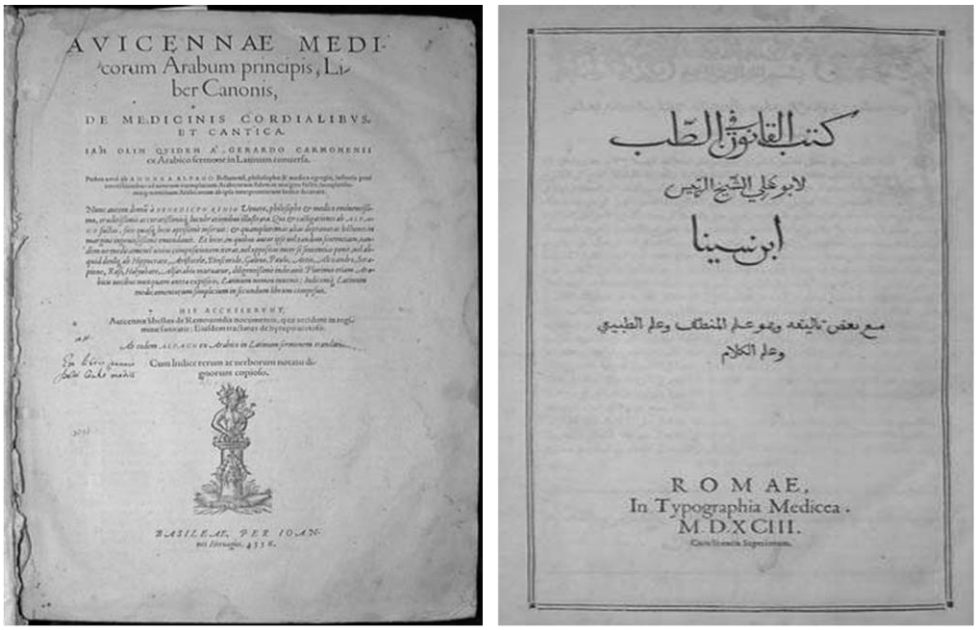
In TCM, Black Seed has been used to kill worms in the intestines, improve digestion, increase sweating to reduce fever, improve urine output, increase menstrual flow, increase breast milk secretion, relieve constipation, relieve asthma, and increase nervous system activity [104, 105]. Black Seed has been used to relieve common digestive system conditions such as stomach pain, spasms, wind, bloating, and intestinal colic [106]. Externally, powdered

black seed blended with sesame oil has been used to treat wounds and haemorrhoids. Moreover, ground seeds mixed with mustard oil were used to treat scabies and remove fleas from the hair [107]. Most of these uses are similar to those mentioned in Greek, Arabic, and Ayurvedic Medicine. This is probably because the knowledge of Greek and Arabic Medicine reached India, that is, the conquest of many parts of China by the Muslim Emperors in the Middle Ages and the migration of scholars from Middle Asia to China, in addition to the contributions of local experts. Modern-day research relevant to the applications of *N. sativa* documented in TCM has been described above.

Black Seed and Arabic Herbal Medicine

Black seed was extensively employed by Arab scholars and physicians in the Middle Ages for a large number of ailments, including 'Sartan' (cancer). Well-known physicians of that era include Ibn-Sina (Avicenna), Al-Razi, Ibn Al-Nafis, Al-Taberi, Al-Magusi, Al-Baitar, Al-Zahrawi, Ibn-Haitam, Ibn-Zuhr, and Ibn-Rushd. The most famous Muslim physician of the Middle Ages was Ibn Sina (980-1037 AD).

Ibne Sina (Abu Ali al-Ḥusayn ibn Abd-Allah ibn Sina), commonly known in English by his Latinised name 'Avicenna, was born in 980 in Kharmaithen **(**near Bukhara), Central Asia (now Uzbekistan), and died on June 1037 in Hamadan (now Iran). Avicenna authored numerous books on medicine, mathematics, astronomy, physics, chemistry, natural sciences, logic, poetry, philosophy, and Qur'anic explanations. One of his famous books in medicine is "Canon of Medicine" (Arabic: Al-Qanun fi' Al-Tibb), which was originally written in Arabic, in five big volumes: I General Theory and practice of Medicine. II Simple drugs (Including Herbs). III Diseases of individual body parts: IV Systemic diseases. Pharmacopoeia [108]. Avicenna's Canon of Medicine was translated into Latin in the 12th century by Gerard of Cremona (1114–1187) and printed in Milan in 1473 and later in 1556 (Figure 9a). The Arabic text was first printed in Rome in 1593 (Figure 9b) [109].



(a) (b)

Figure 9. (a) Title page of the Latin version of the 1556 edition of Avicenna's '*The Canon of Medicine'*. (b) Title page of the first Arabic edition published in Rome in 1593 [110].

The 'Canon of Medicine' remained a textbook of medicine at many universities in the Middle East, Europe, and many parts of Asia (Including Montpellier and Ouvian) in the Middle Ages until the 17th century. It is still used as the main text of Islamic Unani medicine in South Asia. An important Arabic text was printed in Cairo in 1877. Later, the Canon was translated into Russian and published in Tashkent between 1954 and 1960. Parts of the text are also available in French, German, Hebrew, Greek, Persian, and Urdu [111].

Ibn-Sina has mentioned a large number of clinical applications of *N. sativa* in his book 'Qanoon Fi Al-Tib'. Black Cumin has been prescribed to clear warts, freckles, skin scalings, and vitiligo. Also removes pimples, phlegmatic, soft and hard tumours (Incliding 'Sartan', or cancer) when used mixed with vinegar. Its oil applied on skin and scalp beautifies skin and hair and improves hair growth. It has been used to treat heat rashes and insect bites, as well as chronic skin conditions like eczema and psoriasis. Inhalation of roasted Black Cumin kept in a linen cloth is

beneficial in the common cold. Soaked in vinegar for some time powdered and used as a snuff, Black Cumin is useful for treating chronic headaches and facial paralysis. It is useful in treating toothaches when its boiled form is mixed with vinegar, particularly, when the same mixture is used as mouthwash along with the bark of Pine tree. Black Seed in combination with Sodium Nitrate taken orally relieves asthma and bronchitis. The root of Nigella is said to be useful in treating stomach ailments. Black Cumin taken orally is effective as a vermifuge. Prolonged intake for several days with honey promotes the menstrual flow. Similarly, it is beneficial in treating male impotence. When taken with hot water (as a tea?), is useful for bladder and kidney stones. The boiled form of Nigella roots (as a tea) has a diuretic effect. Oral intake of Black Cumin powder mixed with honey eliminates fevers. It relieves cough, acute and chronic, and is also useful for treating asthma. Black Cumin improves digestion and relieves abdominal pain (Stomach pain and intestinal colic). Black Cumin is described to improve general well-being, mood, and memory. It has also been recommended for treating epilepsy and other types of seizures. When burnt, its smoke kills or drives away insects [112].

Studies relevant to the uses of black seed mentioned by Ibn Sina

Most of the studies conducted in the recent past relevant to the use of black seed in various clinical conditions have been discussed earlier, along with its use by ancient Greek, Indian, and Chinese physicians and Prophetic Medicine (Tib-Al-Nabavi). Present-day investigations related to the application of *N. sativa* in cancer treatment are briefly mentioned.

The anticancer activity of *N. sativa* was reported for the first time in the current era, when Black Seed supplementation with standard immunomodulatory drugs showed a many-fold increase in the activity of natural killer (NK) cells in cancer patients [113]. Since then, many studies have been conducted to determine the anti-cancer effects of black seeds, their oil, and their active compounds. Earlier, most studies conducted to evaluate the anti-cancer activity of black seed locally applied black seed extracts prevent formations of papillomata's skin cancer produced by dimethylbenzene/anthracene/croton oil. Intraperitoneal administration of black seed extracts prevented the formation of various soft tissue sarcomas produced by methylcholanthrene in mice. Similarly, oral gavage of black seeds prevented carcinoma formation in rats exposed to methylnitrosourea. In addition to investigations regarding the anticancer activity of black seed in in vivo small animal cancer models, many studies have reported the efficacy of black seed extracts and active compounds on various types of human cancer cell lines, including 3T6 fibroblast line, Ehrilch's ascites carcinoma, Dalton's lymphoma ascites, sarcoma-180 cells, and SW-626 colon cancer cells. The anticancer properties of black seeds, their extracts, and their active components have been reviewed by Randhawa and Alghamdi [7].

Recent studies on the elucidation of the mechanism of action of thymoquinone (TQ), an active principle of the black seed, revealed that TQ destroys cancer via an increase in apoptosis, arrest of the cell cycle, production of reactive oxygen species, blockade of the generation of new blood vessels in the cancer tissue, and prevention of the distant spread of cancer. Black seeds also induce host immune mechanisms to kill cancer cells. Moreover, black seed counters the various side effects of allopathic anticancer medicaments because of its antioxidant and cytoprotective properties [114-118].

Conclusions

Nigella sativa (Black Seed) has a long history and wide geographical distribution. Its therapeutic potential was known to the Hittites (1650 BC) in Anatolia (Now Turkey) and Egyptian Pharos, particularly Tutankhamun (1341–1323), and has been mentioned in old religious literature, such as the Book of Isaiah (Old Testament of Bible, 8th century BC) and was prescribed by ancient Greek and Roman physicians, including Hippocrates, Dioscorides, and Galen (460 BC to 216 AD). Black seeds have a noteworthy status in the primaeval Arabic, Ayurvedic, and Chinese systems of medicine. Important historical landmarks in the Middle Ages emphasising its medicinal use are the Hadith of Prophet Muhammad (Peace and blessings be upon him), 571–632 AD, "Use the black seed, for it is a cure for all ailments except death" (Al-Bukhari) and its mention in "Canon of Medicine", a well-known textbook of medicine by Abu Ali Ibn Sina or "Avicenna" (980–1037 AD). In the present era, numerous scientific studies have elucidated the pharmacological properties and therapeutic potential of this plant. This review aims to bridge the gap between traditional uses and contemporary scientific discoveries.

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