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Mirror of Research in Veterinary Sciences And Animals

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Animal ectoparasites and its zoonotic impact on human's health

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Abstract

Ectoparasites of animals (farm animals, rodents, and birds) such as mites, ticks, fleas, and lice able to infest humans. It is considered as zoonotic arthropod infections of humans and plays an essential role in the transmission of several pathogens. Zoonotic diseases define as infections of animals

that are naturally transmissible to humans. Moreover, these ectoparasites from different species of animals are frequently recorded as biting of humans and commonly leading to the development of extensive and severe allergic rashes. Likewise, strains of animals *Sarcoptes scabiei* from the farm, companion, or even wild animals can also infest humans. *Cordylobia anthropophagi* and *Dermatobia hominis* the causative agents of myiasis in Africa and Latin America, respectively, are other zoonotic arthropod infections of humans. These infections were commonly reported in travelers and refugees from these regions. It is worth to mention here, although lice are very host specific and accordingly, lice of animals do not attack humans (vice versa). However, ticks are mostly not very host-specific, and therefore it attacks humans; moreover, some species causing tick paralysis and many responsible for transmitting viral, bacterial, and protozoan diseases of animals to humans. Review of literature revealed scarce publication regarding the animal ectoparasites and its zoonotic impact on humans. Consequently, this review article emphasis on animal ectoparasites and its zoonotic impact on humans, particularly mites, and ticks the more common ectoparasites.

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Keywords: Animal, Ectoparasites, farm animals, tick paralysis, zoonotic impact.

1. Mites

Mites are related to ticks, spiders, and scorpions. Its body is divided into two rather than three parts, and in contrast to insects, they don't have antennae. The mites have 6 legs, but the adult has 8 legs and is smaller than ticks. These animals engage the most diverse ecological niches, such as Demodex mites that multiply in the sebaceous glands of human eyelashes. The causative agent of scabies is the *Sarcoptes scabiei*. It is *acati*, *Sarcoptes bovis*, and *Sarcoptes equi* in dog, cat, cow, and horses, respectively (Alasaad *et al.*, 2009; Alasaad *et al.*, 2011; Roncalli, 1987). A mite infestation cause

scabies. It is frequently sexually spread. It dates back to ancient times but remains an exciting parasite for study in clinical practice and public settings. Its record is one of the centuries of slow growth to recognize the mite and to lastly, create its relation to the clinical signs of pruritis with several fluctuating appearances and diverse epidemiological outlines (Currier and Ceilley, 2010).

1.1. Definition of Scabies

The Latin words scabere to scratch means scabies. It is a condition characterized by colonization of the mite *Sarcoptes scabiei* on the skin of an animal or human host after skin to skin contact with a donor host. The pruritis results after some time, commonly three to six weeks of infestation, which remains for a long period or until the treatment of the patient. In many developing countries, scabies is a common illness affecting large segments of the population, and is similarly found worldwide in sexually active young adults and, rarely, in their children, owing to hands-on care. A more contemporary phenomenon is the appearance of scabies in institutional populations, particularly immunosuppressed people and in long-term older people living in care facilities (Martin and Wheeler, 1979; Currie and McCarthy, 2010). Moreover, sarcoptic mange in animals remains a problem in most areas of the world and considers as the most important zoonotic diseases.

1.2. The history of scabies

The history of scabies is an extended one and re-observed smartly in numerous literatures during the first half of the 20th century by Dr. Reuben Friedman, Temple University in Philadelphia. He classified the history in three periods: Ancient the Pre-Acarian, Medieval the Acarian, and Modern the Post-Acarian (Friedman, 1934). The investigators (Aristotle and Galen) from Greek and Roman, valued the “contagious” property of the scabies illness. The term acarus was firstly used by Aristotle to describe an animalcule so minute as to be uncuttable or indivisible.” The Roman, Celsus, designated the scabies of sheep and its treatment similar to for humans at the time with a combination of sulfur and tar (Friedman, 1934). The Avenzoar’s work , subsequently in Spain, described the mites as: “The little flesh worms which crawl under the skin of the hands, legs, and feet, and there grow pustules full of water, are termed syrones, asoabat and asoab: so tiny are these animals, that they can hardly be seen by the strongest of vision ” (Friedman, 1934). However, Avenzoar did not particularly associate the mite with the disease illness. Later on, scabietic lesions were described by a number of researchers throughout the 13th–16th centuries, conversely miscarried to create the connection of causality.

In the 17th century, Hauptman formed unsatisfactory drawings of the mite. Moreover, in 1687, an Italian naval physician (Giovanni Cosimo Bonomo), collaborated with Giacinto Cestoni, a pharmacist, studied skin condition in sailors and delivered a more precise drawing of the acarus mite.

Consequently determining and creating the parasitic nature of scabies as well as its treatment (Warburton, 1920). In 1746, Linnaeus, the Swedish naturalist, classified the mite as *Acarus human-subcutaneous* (Linnæus, 1748). Lastly, DeGeer, a Swedish naturalist, draw the first very precise diagram of the mite. Moreover, his name remains with the mite nomenclature, that is, *S. scabiei* (DeGeer). This acarine period was closed with the presence and description of the mite at hand, but the main belief, though, excluded the acceptance of the cause and effect relationship.

In 1834, a furthermost studied event in the history of scabies occurred and a mite from a young female patient suffering from “the itch” were collected by Simon Francois Renucci, after several years of controversial faculty argument. He achieved the task with a needle probe technique for removing mites. At the late 19th and early 20th centuries, the post-Acarian period revealed continual advances with raising alertness of distinctive scabies from other pruritic skin conditions. The first dermatologist was from Vienna (Ferdinand Ritter von Hebra), who described different scabies stages of infestation and mites life cycle after seeing and treating over 40,000 cases. He also assumed that species from a variety of animals and humans were essentially one species. However, the misunderstanding was continuous at this time due to the environment remained a means of transmission in some substantial ratio of cases. In the United Kingdom, extensive work to understand scabies was done by an entomologist Kenneth Mellanby (Mellanby, 1972). Mellanby was bespoke by the United Kingdom to study scabies from the standpoint of defining measures for the disinfection of the milieu. This demand appeared due to major scabies incidents in the United Kingdom during the second world war both in civilians in over- crowded families and in servicemen. The crucial request wanting to explain was to what level fomites were a risk to unchanged peoples and how best to disinfect them. Mellanby originally studied scabietic soldiers and found that the overall mite load in utmost cases was very small, that is, less than 10, although a few had extensive mite burdens (Mellanby, 1972). As a final comment, Mellanby’s technique of needle probe removal of mites is not far from a clinician’s everyday abilities.

1.3. Scabies of the animal

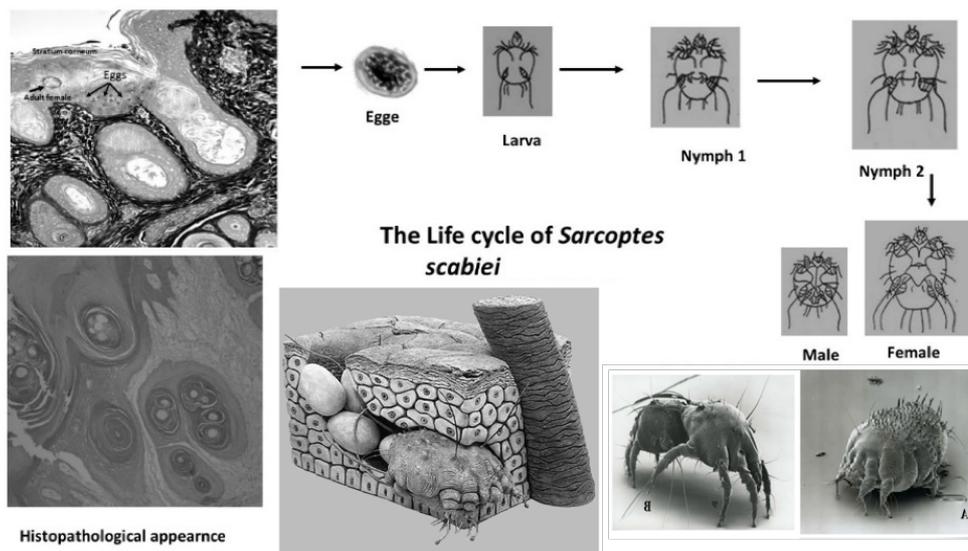
Cnemidocoptes, *Chorioptes*, *Psoroptes*, *Notoedres*, *Otodectes*, and *Sarcoptes* are the six genera of mites that originated on animals. Meanwhile, Sarcoptic mange has been described from 10 orders, 27 families, and 104 species of domestic, free-ranging, and wild mammals (Pence and Ueckermann, 2002). The works and research on mange, particularly sheep scab, began circa 1800. Moreover, the Walz’s work (veterinary surgeons) were cited as being useful (Walz, 1809), who correlated the illness to mites (*Sarcoptes* can be the cause of sheep scab but more usually *Psoroptes* mites). It is worth to mention that the veterinary metropolitan was the chief of the arena of human medicine in identifying mites as the reason of many scabies-like skin disorders, earlier than Renucci’s “rediscovery” of the mite from a human patient.

In 1786, Johann Ernst Wichman (German physician) published an essay on scabies titled “Aetiologie der Kratze,” that delivered full drawings of the mite. He concluded that mange in sheep, similar to humans, is due to mites. The first collection of mites from horses infested with mange was done by professor Jean Baptiste Gohier (1776–1819 AD) and his colleagues St. Didier, at the Veterinary School in Lyons, France, and this observation was reported by Roncalli smart review. Moreover, *Dorfeuille*, from the Veterinary School of Lyons, can also be considered one of the first scientists to have realized and paly roles in discovered the presence of mites in mangy cattle (Roncalli, 1987). Nevertheless, the development in the detection and controlling of animal scabies identically that of human medicine during the subsequent decades and the 20th century.

1.4. Epidemiology of humans scabies

Scabies epidemics appear at vague secular cycles that stay for about 15 years' period with the highest periods in the past century being 1915–1925, 1936–1949, and 1965–1980. The Pandemics of scabies are linked with lack and poverty, poor hygiene, increased sexual interest, and demographic factors accompanied by migration and wars being significant effects. In developed countries, the longer survival of immunosuppressed patients has served to expand mite burdens and boosted transmission. There are differences in the infrequent of mange infection in the United States, African- Americans, and the total males outnumber females, though this is not reliable with percentages in other countries (Orkin, 1983; Green, 1989). During scabies epidemics, the incidence of scabies reached 7 to 18 % / 1000 residents in Europe, according to Manfred Green. However, it is reduced to 0.5 to 2 per 1,000 during nonepidemic periods. Moreover, the higher incidence has variability according to seasonality and falls during winter months. There is also variability according to the age distribution, but with the greatest cases occurring between the ages of 15–45 years. Another factor such as sex differences, sociocultural factors, including sexual risk patterns within individual countries, affected the incidences of mange. Many places such as hospitals, long-term care facilities, and occasionally schools are served as foci for infection (Heilesen, 1946). Many researchers investigate the methods that use by the mites to transfer itself to the new host, and they found that immature mites frequently walk on the surface of the skin and opportunistically alight on a new host (Heilesen, 1946). Moreover, the adult fertilized female mites were important in transmission. The life cycle of the mites is presented in Figure 1.

A large proportion of immunosuppressed individuals such as HIV patients, the elderly, organ-transplant recipients, and oncology patients, the mite load in some individuals may be relatively high, spreading to extraordinary numbers as in the rare cases of hyperkeratotic or crusted scabies. Nosocomial outbreaks also occur, with secondary transmission to healthcare workers and tertiary transmission to other patients and their household members (Wright *et al.* , 2001).

Figure 1: The life cycle of *Sarcoptes scabiei*

1.5. Perceptions of *Sarcoptes scabiei* Evolution

Sarcoptes scabiei is the cause of sarcoptic mange in livestock, wild, and companion animals, as well as scabies in humans. The significant morbidity and occasional mortality in severe cases occur due to mites infestation. The host-related inhabitants of *S. scabiei* have been taxonomically divided into morphologically indistinguishable changes that have a high grade of host specificity and low degree of cross-infectivity (Fain, 1978). Conversely, the monospecific of these host-specific strains of *S. scabiei* is controversial, and up-to-date studies are discovering if they are identical or diverse species. Many factors are complicated in the case of *S. scabiei*, these factors are as follow: the indication of obvious cross- infectivity among hosts verified in emerging epizootics in sympatric wild animal host inhabitants (Arlan *et al.*, 1984) the vague morphology of the host-associated inhabitants, incomplete or no indication for cross-infestations occurring among hosts in trial reports, and finally indication of immunological host-specific and cross-reactive molecules (Arlan *et al.*, 1996; Haas *et al.*, 2005). The understanding of the genetic aspects of Sarcoptic host-associated populations significantly has been improved due to the application of molecular markers. Moreover, the molecular data is providing insight into both host selection and host-mediated influences on *S. scabiei* population structures (Walton *et al.*, 2004; Walton, *et al.*, 1999; Alasaad *et al.*, 2011). The existing indications reveal that evolution due to adaptation of the Sarcoptes diversities looks to be powerfully connected to the phylogenetic parallel with the host species (Walton *et al.*, 1999). Walton *et al.*, (1999) were shown the considerable proof of narrow gene flow between sympatric inhabitants of human and dog mites in scabies endemic, indigenous societies in Australia. They were demonstrating for the first, using both nuclear and mitochondrial markers, genetically different host-associated populations. The consequences of this study were then retained to drive changes in regional public health strategy

(Walton *et al.*, 2004). Later, several molecular studies were exploring the population dynamics and genetic epidemiology of various wild animal host-associated *S. scabiei* populations, using the same multilocus microsatellite markers (Alasaad *et al.*, 2011; Fain, 1978; Arlian *et al.*, 1984). These studies show further proof that *Sarcoptes* is not a distinct panmictic population and approves genetic subdivision according to host with secondary sub-assembling correlated to the geographical location within host clusters. Additionally, population structure studies also shown chronological constancy in the genetic variety of *Sarcoptes* mites (Walton *et al.*, 1999; Anderson *et al.*, 1997). Concerning evolutionary interactions, molecular records also propose that there is widespread evolutionary variance between human-associated mite populations and other animal-associated mite populations and that these populations may not have shared a common progenitor for 2–4 million years (Walton *et al.*, 2004). Nevertheless, many evolutionary questions related to *S. scabiei* continue to be resolved. When studying carefully associated parasitic species or populations, many gene characters are shaped by the demographic record of the host population and the effect of the latter on the degree of gene flow and recombination on the parasite population structure. Insertion of scabies mites into naive populations result in originator effects and population sub-structuring. Moreover, there is clear genetic variation between *S. scabiei* mites found from different individuals of the same host species in the same municipal; mites with like genotypes were more often found within the same host (Walton *et al.*, 1999). This nonrandom dissemination within individual hosts is characteristic of other parasite populations, apparently because of colonization by limited numbers of initiators. Improbability in the clarification of phylogenetic connections in molecular data can also be due to the diverse, informative values and consistency of sequences, recombination events, and the possible persistence of ancestor sequences in populations. Moreover, the molecular studies exploring the evolutionary connection of *S. scabiei var hominis* with animal-associated populations have not as hitherto been published. Nevertheless, mitochondrial analyses, limited to investigations on the phylogenetic lineages of animal associated Sarcoptic mites, revealed narrow or no evolutionary sub-structuring according to host (Anderson & Jaenike. 1997; Zahler *et al.*, 1999). The results of these later analyses may be due to the use of vague regions of mitochondrial DNA, or evolutionary likeness of animal-derived *Sarcoptes*. While not endorsed, the current scientific harmony is that humans—and protohumans before them were the main host for *Sarcoptes* mites (Berrilli *et al.*, 2002).. When humans domesticated various species of animals, of which the dog probably was the first (over 14,000 years ago), behavioral transmission, for example, domesticated animals escaping and transferring to wild animal populations, probably occurred. Identifying that domestication per se tends to decrease immunocompetence, domesticated animals may have been more vulnerable to infections, thereby raising the chance of mites adapting to new hosts. Domestic animals that runaway, in turn, most likely then infected several wild non-domesticated species. Phylogenetic relatedness can help to inform solutions to many parasitic diagnostic, treatment, and epidemiological control problems. The molecular phylogenetic studies, demonstrating genetically differentiated human and

animal host-associated mite inhabitants, reflect efforts at emerging serodiagnostic tests. Serodiagnosis of scabies in animals can be diagnosed by Enzyme-linked immunosorbent assay (ELISA) kits, using mite extracts of *S. scabiei var. Vulpes* (Walton *et al.*, 1999; Hollanders *et al.*, 1997). But, these tests have little sensitivity for scabies in humans (Walton *et al.*, 1999). Currently, the confirmative diagnosis of human scabies infection requires the collection of skin scrapings and identification of a mite, mite parts, eggs, or mite fecal pellets. While this method is highly specific, the diagnostic sensitivity is low due to the low number of mites present in ordinary scabies. Currently, the sensitive detection of IgE reactivity in humans has been established with genus-specific scabies mite epitopes for differential diagnosis of scabies mite allergy from an allergy to house dust mites. The extent of the growth of resistant mechanisms to chemotherapy may also be restricted or enhanced by *Sarcoptes* population genetic sub-structuring. Evidence for *de novo* ivermectin resistance has arisen following intensive treatment of crusted scabies patients in Darwin, Australia (Currie *et al.*, 2004; Mounsey *et al.*, 2009). The growing of *in vitro* tolerance of *S. scabiei var hominis* has also been connected to mutations in target voltage-sensitive sodium channel genes. Information on phylogenetic connections of *Sarcoptes* host-associated inhabitants is important, as likely developing resistance may occur in sympatric inhabitants via recombination or horizontal gene transmission. The presence of a limitation to free gene exchange between host-associated populations of scabies mites suggests that effective controlling practices can be established for targeted inhabitants (Walton *et al.*, 1999). Evolutionary research and population dynamics may also contribute to *Sarcoptes* vaccine growth. In the developed countries and some wild animal populations, transmission of the scabies mite is probably not density-dependent but rather based more on sexual or familial transmission. If so, the efficacy of a vaccine may prove debatable. This is in contrast to disadvantaged communities with high population densities and endemic scabies, in which a vaccine would be highly advantageous. However, changing environments such as increasing use of institutionalized care for the elderly and day care for the very young, establish susceptible populations with high population density, and reduced immunity. Evidence of increasing institutional outbreaks of scabies has been reported in the literature (Walton *et al.*, 2004; Walton *et al.*, 2010). Usually, vaccination is most effective in small inhabitants facing very high infection rates. Design of future control plans for scabies will be enhanced with growing evidence on the epidemiology and evolutionary understanding of the *Sarcoptes* mite in multiple-host systems, and the vaccination or treatment procedures are tending to be most effective under diverse illnesses. The inflammatory reaction to scabies mites may also have a role in development. The severe parasitization of the skin in crusted (Norwegian) scabies is similar to the sarcoptic mange of animals, and it is not unexpected that at one time cases of crusted scabies were believed to be of animal source. Ordinary scabies displays a mite burrow as diagnostic but never appear in crusted or animal scabies, and is similarly not appear on human skin in transient infestations of animal varieties of scabies mites. The amplified strength of inflammation in crusted and animal scabies may reveal changes in host immunogenetics, changes in gut microbial and diet affecting immunity, and/or the effect of

cross-reactivity with other parasites leading to boosted susceptibility and sensitization. Classical transmission research record an early increase in scabies mite numbers after primary infestation with a gradual decrease as host immunity develops (Morgan & Arlian, 2010). Morgan & Arlian, (2010) propose that the coevolution of the mite with the mammalian host has preferred the choice of parasite adaptations, allowing it to down-regulate aspects of the host's innate and immune responses, as seen in ordinary scabies. Experiments on human skin equivalents demonstrate that scabies mites can downregulate the expression of many cytokines and adhesion molecules of skin epidermal keratinocytes, dermal fibroblasts, and dermal microvascular endothelial cells (Walton *et al.*, 2010). Additional studies exploring evolutionary interactions can also aid in explaining alterations distinguished in innate and antibody-dependent and independent immune activation events in ordinary, crusted, or animal scabies (Walton *et al.*, 2010). Increased information on the structural and functional mechanisms of immune evasion and survival by different host-associated parasite inhabitants could well result in enhanced control and controlling.

1.6. Human clinical scabies: detection and controlling

The most clinical's challenging problems for general physicians and experts likewise remains the scabies. There are different clinical presentations of human scabies. The ordinary scabies usually appeared in healthy adults in whom sexual transmission plays an important role, with consequent between familial contact spreading, particularly to children. However, these patients have only a little mite load averaging ~10 adult female mites/patients. Nevertheless, the immunosuppressed patients show the rare covered or keratotic lesion of scabies that have very heavy mite loads and may number in the hundreds or thousands, often with little or no pruritis. The atypical crusted is the third form of scabies that seen in nursing homes, institutions, and HIV/AIDS affected patients that present with an considerable mite problem and characteristic pruritis. The pseudo- or psycho-scabies is the fourth form that appears in effectively treated patients and institutional workers or family members accompanying with recognized scabies patients, who though not infested, suffer from misunderstandings as a purpose of the "power of proposal." This last group is not to be confused with the identified persistence of inflammation (and itch) that is not unusual following effective therapy in scabies patients and that can last for several weeks and irregularly longer. It is very important to mention that scabies is at once the easiest and most difficult diagnosis in medicine and all four forms of scabies present challenges to the clinician. The extensive contact of a noninfected person with an infested patient lead to transmitting of mites that results of scabies. The mites males fertilized the adult female mites. This female then burrows into the stratum granulosum of the skin, laying zero to four eggs every day along more than six weeks before it dies. Two to four days after eggs are laid, larvae hatch and cut through the skin surface and start to excavate new burrows. After three to four days, the larvae molt into protonymphs, which two to three days later molt into tritonymphs, from which an adult male or female develops after a further five to six days. The

whole cycle takes about two weeks (Figure. 1). Sensitization occurs to mite metabolites after a period of three to six weeks, resulting in pruritis. Sensitization to mite antigens can be demonstrated a month after following primary infestation, with both humoral and cellular responses evident. Most essentially, the ability of these patients to transmit scabies during this “incubation period,” leading to the endorsement of treating all members in a household with some exclusions. The intrafamilial transmission considers as the most common following sexual transmission among adults that reported in different epidemiologic studies.

1.7. Clinical features

Scabies in adults and older children frequently appears as an extremely pruritic rash, typically more apparent at night. The rash is measured to result from combinations of two processes: papular or vesicular lesions happening at the place of burrows created by adult and larval mites and a widespread pruritic and erythematous papular eruption that is unrelated to apparent individual mites and that is thought to be an immunological response (Currie, 2005). Regions most habitually exaggerated are where the stratum corneum is most thin with few hair follicles, commonly including the interdigital webs of the digits, flexor surface of the wrist, extensor surfaces of the elbows, and other similar areas but seldom in the face, head, and neck. Children and adults in tropical regions repeatedly have the involvement of palms, soles, face, neck, and scalp. The classic sign of scabies is the burrow or more frequently papules. Burrows appear as grayish, reddish, or brownish lines, 2–15 mm long. Egg cases and mite fecal pellets are present inside the burrow. The papule at the burrow surface is usually small and erythematous, often attacked or concealed by a small blood clot. Children and adults in tropical areas, as well as patients who wash regularly and practice excellent personal hygiene, may not display burrows, thus challenging clinical doubt and correct diagnosis (Currie, 2005). Confusing the clinical impression is the fact that affected skin may exhibit secondary bacterial infection. Scabies frequently analogous to syphilis and may display a variety of other manifestations. These are involving scabies “incognito” in patients who have received topical or systemic steroids, nodular scabies with reddish-brown pruritic nodules present, and infrequently crusted or hyperkeratotic scabies, mainly in patients who are elderly or immunosuppressed. The patient with crusted scabies has enormous mite burdens in their living environment, clothing, and bedding, posing a risk to family and caretakers (Carslaw *et al.*, 1975; O’Donnell *et al.*, 1990). This kind of scabies is commonly called as “Norwegian” scabies, that firstly described by Danielsson and Boeck it in Norwegian leprosy patients in 1848 (Danielsson & Boeck, 1848).

1.8. Diagnosis and treatment

The diagnosis of scabies is commonly challenging because scabies is “at once the easiest and most difficult diagnosis in medicine.” A final diagnosis is not straight as the typical skin tunnels regularly only become observable after

secondary infection or eczematous reaction. The scabies is defined as a cause of acute glomerulonephritis as a consequence of the superinfection of the lesions by β -hemolytic streptococci (*Streptococcus pyogenes*). However, there is doubt about this. Clinically, the existence of burrows is practically diagnostic, but as noticed earlier, they are not always found. The involvement of other family members is very suggestive, according to previous records (Orkin, 1971; Orkin, 1975). Skin scrapings and exfoliative cytology are the most important methods for diagnosis, where the suggestive skin lesion is lightly scraped to remove the superficial epidermis and the oil deposited on a microscope slide. It is essential to collect samples from numerous lesions onto one slide, and if adequate doubtful lesions are found, to make at least four to six slides. Mites and eggs should be examined under low power of 40X methodically. The *Sarcoptes* mites appear as turtle-shaped, and the examiner should not be confused with very elongated *Demodex folliculorum* or *D. brevis* mites on patients. A second method is to tease out a mite with a mounted needle probe to better view the process and doubtful location within a papule or burrow. This part can be better defined with the burrow ink test, in which an uncertain lesion is rubbed with a blue or black felt tip pen and the area is then washed with an alcohol pad with capillary action, drawing the ink into the region thus creating a distinguishing dark, zigzagged line passing across and far from the lesion. Lesions can also be curetted or biopsied if needed. The scabies is responsible for provoking papular, pruritic skin rash. The itching also occurs at the sites where the mites themselves are found, e.g., between the fingers, wrists, elbows, genitalia. Meanwhile, body parts that are not infested by scabies mites are also showed rash. Backsides, shoulders, groin, ankles, and arms can become itchy. The rash nearly not occurs on the head, palms of the hands, and soles of the feet in classic scabies. Mite allergens are the cause of the patient hypersensitive that lead to the appearance of the rash. In a person who has never been infested to scabies, the rash commonly arises 4-6 weeks after infection. However, in previously infested people, it occurs much more rapidly, sometimes within just a few days. The symptoms and lesions of scabies can persist for weeks (e.g., scabies nodules on the scrotum and penis), despite effective treatment. Moreover, the hypersensitivity to the scabies mite does not disappear immediately after the death of the parasite. In veterinary medicine, the serologic tests are available and are being assessed for humans but could be unclear in distinguishing current infections from the previous infestation. Moreover, eosinophilia and high IgE levels are very common in scabies, which is also realized with many other endemic parasitic infections (Currie, 2005). Skin scrapings stay the “gold standard” of scabies diagnosis and that needle probe techniques can be done by a clinician who obtains knowledge with the method in highly endemic locations. The topical acaricides are the common scabies therapy, though oral ivermectin is increasingly being used in certain situations, most remarkably for crusted scabies). In Great Britain and the United States, the topical permethrin and oral ivermectin are found recently as the reasonable best medication options. The preventive treatment is also recommended in close sexual and nonsexual contacts.

1.9. Zoonotic aspects of camel’s mange

Mange of the camels is one of the most important zoonotic diseases (Schillinger, 1987; Higgins, 1983; Richardd, 1979). Camelids mange is caused by *Sarcoptes scabiei* var. *cameli* (Richardd, 1979). The recognizable clinical symptoms of the disease in camels are pruritus, hair loss, and loss of condition (Curassong, 1947; Leese, 1927; Rathore & Lodha, 1973). Additionally, the acute form can lead to a subacute or chronic form (Rathore & Lodha, 1973). Direct transmission of camel's mange to man is widespread and occurs due to the close and maintain contact of the herdsmen with their camels, resulting in the condition in man termed pseudorabies (Higgins, 1984; Fain, 1978; Kraft, 1956). The transmission from camel to man usually occurs during milking. The more common sites of the lesions are seen in the forearms, especially in the hand's interdigital spaces, the flexor surface of the wrists, the elbows, and axillary folds. Besides, the lesions occur between the thighs in the case of camel riders. Once a herd has been infested, continuous reinfections arise that make a difficult assessment to whether the disease in man is self-limiting, as described for sarcoptic mange transmitted from other animals to man (Zumpt & Ledger, 1973; Chakrabarti, 1985). To control this zoonosis of the pseudoscabies in humans, it is important to treat both camels and men. The treatment to be preferred in man is hexachlorocyclohexane (Chakrabarti *et al.*, 1981). There are several factors responsible for the unsuccessful use of organochlorine and organophosphorus acaricides in camels such as lack of water, incorrect preparation and inadequate application of washes and sprays as well as nomadic living conditions which prevent repeated treatments. Therefore, the alternative is the subcutaneous injection of ivermectin at 0.2 mg/kg body weight (Meigel, 1979). This treatment not only kills the sarcoptic mites but most of the gastrointestinal nematodes of the dromedary as well (Hashim & Wasfi, 1986).

1.10. Conclusion

In conclusion, the persistence of scabies is dated back to ancient times, and it's spreading back in evolutionary "deep time" as an assumed uniquely human parasite that expanded its host base to animals following domestication and later wildlife species. The scabies leftovers as a very severe dermatological condition in third world population, particularly in the institutional, and sexually active young adults with numerous partners and their household members. The development of this problem is some parasites may be more successfully tackled with molecular studies of its genetic structure and immune responses, leading to more effective diagnostic abilities to address the ever-challenging objectives of effective treatment and control.

2. Ticks

2.1. Introduction

Globally, ticks (Figure.2) are currently measured to stand second only to mosquitoes as vectors of human infectious diseases. Every tick species has favored ecological circumstances and biotopes that regulate the environmental and geographical circulation of the ticks and, accordingly, the danger parts for tickborne illnesses. This is precisely the instance when ticks are vectors and

reservoirs of the pathogens. Subsequently, in 1982, the cause of Lyme disease was recognized as the *Borrelia burgdorferi*, and 15 ixodid-borne microbial infectious pathogens have been defined in the world, including 4 species of the *Borrelia burgdorferi* complex, 8 rickettsiae, and 3 Ehrlichia. Ticks are obligatory hematophagous arthropods that parasitize every class of vertebrates in almost every region of the sphere (Boyce *et al.*, 1984). About 869 species or subspecies of ticks were reported in 1996 (Sonenshine, 1991). There are two main tick families that are varied both structurally and in their life cycle. These families are as follow:

- The Ixodidae, or “hard ticks,” so named for their sclerotized dorsal plate, that is the most significant family in numerical terms and medical importance, and comprises 2 major groups, the Prostriata, and the Metastrata

- The Argasidae, or “soft ticks,” so named for their flexible cuticle (Boyce *et al.*, 1984). Two subfamilies are currently recognized in the Argasidae: the Argasinae and the Ornithodorinae (Roncalli, 1987).

While, the third family, the Nuttalliellidae, is represented by only a single species that is limited to southern Africa.

The lifecycle of ticks pass into three 3 stages:

- the larval,
- nymphal
- adult (male and female).

Ixodids have an amount of features that develop their vector potential and feed for relatively long periods (several days), through which they continue tightly attached to the host. Moreover, their bite is commonly painless, and they may go unseen for prolonged periods. Each phase of the tick suckles only once, and this feeding may include an abundant diversity of vertebrates that inhabit extremely diverse habitats (Boyce *et al.*, 1984). Instead, Argasids suckle briefly and often, usually on a single host species. They tend to live in dry areas, and most species live in sheltered sites near their hosts (Boyce *et al.*, 1984). For thousands of years, ticks have been recognized as human parasites that were recorded by ancient Greek writers, including Homer and Aristotle (Boyce *et al.*, 1984). Ticks were confirmed for the first time to transmit infectious agents at the end of the 19th century. *Boophilus annulatus* were proved to transmit the protozoan *Babesia bigemina*, the cause of Texas cattle fever. Ticks were accused as vectors of human bacterial diseases at the beginning of the 20th century. Later on, ticks were approved to transmit *Borrelia duttonii* (Tick relapsing fever) (Sonenshine, 1991), and Ricketts (Dutton & Todd, (1905) and *Rickettsia rickettsii*, the agent of the Rocky Mountain spotted fever. The first cases of Mediterranean spotted fever were recorded in Tunis by Conor and Bruch (Ricketts, 1909), and the responsibility of *Rhipicephalus sanguineus*, the brown dog tick, in the spreading of the disease was proven in the 1930s (Conor & Bruch, 1910). The epidemiology of tularemia and the role of blood-sucking arthropods, including ticks, were reported by Francis (Brumpt, 1932) in 1929. Many protozoa, viral, and bacterial tickborne diseases were defined in animals and humans (Francis, 1929) following World War II. Lyme borreliosis disease due to *Borrelia burgdorferi* was described (Sonenshine, 1993.) in the 1980s. Moreover, the disease is recently appeared as the most important vector-borne disease in Europe and the United States. Meanwhile, some emerging tickborne

rickettsioses have been recorded from around the world (Johnson *et al.*, 1984), and bacteria of the genus *Ehrlichia* have become approved as tickborne human pathogens in the United States and Europe (Raoult, 1997). Ticks can act not only as vectors, but also as reservoirs of tick-transmitted bacteria, involving spotted fever group rickettsiae, recurrent fever *borreliae*, and *Francisella tularensis*. Ticks are transmitted bacteria in two ways as follows:

- The transstadially (from stage to stage from larvae to nymphs and adults)
- The transovarially (from one generation to the next via the female ovaries).

There are best ecological circumstances and biotopes for each tick species, and these establish the geographic spreading of the ticks and, therefore, the hazard areas for tickborne diseases, chiefly when ticks are equally vectors and reservoirs of pathogens. There are various families of ticks, and these are as follows: the Ixodidae, or “hard ticks” (694 species), the Argasidae, or “soft ticks” (177 species), and the Nuttalliellidae that represented by a single species confined to southern Africa (Boyce *et al.*, 1984; Walker & Dumler, 1996; Oliver, 1989).

The common concept of the longstanding development of ticks is built on theories suggesting that structural, biological, and genetic variations of ticks show alterations related to the strength of the hosts and host specificity (Hoogstral & Aeschlimann 1982; Klompen *et al.*, 1996). The gene sequence investigation of nuclear rDNA and mitochondrial are applied to detect phylogenetic connections between ticks. Studies with incomplete sequences of the 16S rDNA mitochondrial gene provided results that were variable with conventional phylogeny; the analyses conserve that the Argasinae are not monophyletic but are an associated cluster of the hard ticks (Klompen *et al.*, 1996). Additional reports that applied incomplete sequences of nuclear rDNA genes have consequently described analogous outcomes (Black, Piesman, 1994). Examination of these sequences, nonetheless, often shows no variances among associated species and thought those fitting to different genera, for example *Rhipicephalus pusillus* and *B. annulatus*. The comparisons of sequences of the mitochondrial 16S rRNA (Crampton *et al.*, 1996) and, more recently, the 12S rRNA genes have been clarified as valuable approaches to analysis the phylogeny of closely connected species. Though they also allowed some associations inside the Rhipicephalinae and the closely related species of the genus *Rhipicephalus* to be determined, the phylogeny of members of the Metastriata yet leftovers vague, and studies of additional genes are essential.



Figure.2. Shows different stages of ticks

2.2. Ixodidae or Hard Ticks

These ticks have a large-body-size (2–30 mm) acarines. The nymphs and adults possess 4 pairs of walking legs, while larvae have only 3. Dissimilar insects, all stages have no antennae, and their bodies are not separated into a distinct head, thorax, and abdomen (Boyce *et al.*, 1984; Mangold *et al.*, 1998). The frontal part of the body, the capitulum, bears the mouthparts, involving cutting organs, sensory organs, and a median immobile organ (the hypostome) with numerous recurved teeth that anchor the tick to the host's skin. The ixodids are characterized by the presence of the scutum (sclerotized plate) on the dorsal surface of the body, and the residue of the body is capable of enlarging during feeding (Boyce *et al.*, 1984; Mangold *et al.*, 1998). Ticks have a circulatory system, that bathed and all organs and tissues by a circulating fluid, the hemolymph (Boyce *et al.*, 1984; Mangold *et al.*, 1998). Eyes are absent in many ticks. However, ticks have a diversity of marginal sensory structures. They include hair-like structures on the body, legs, and mouthparts, the sensory complex located on the dorsal surface of the tarsus of leg I, that encloses Haller's organ (a group of olfactory and gustatory receptors). These sensory organs are vital in allowing ticks to find their hosts and also to interact with other ticks.

2.2.1. Ecology and Life cycles

Classically, ixodid ticks develop a 3- host life cycle, with each feeding stage of the tick (larva, nymph, and adult) taking a single host (Boyce *et al.*, 1984;

Francis 1929; Mangold *et al.*, 1998). Every stage of the tick looking for a host attaches and then feeds over several days. Once replete, the tick separates and dropping from the host, locates in a resting place where it can digest its blood meal and molt to the next feeding stage, or enter di-a pause, (a state characterized by reduced metabolism and delayed development). In a few species, the juvenile forms may persist on the host during molting. Commonly, adult males feed only briefly and sparingly, and some do not feed at all. Commonly, the mating occurs on the host. Subsequently, the females separate and drop off the host to digest their blood meal. They then lay their eggs, from 400 to 120,000 differing on the species, in a sheltered milieu and die (Boyce *et al.*, 1984; Francis 1929; Mangold *et al.*, 1998).. Pheromones play an important role in the behavior of ticks and accelerate ticks' discovering their hosts and their mates. They involve assembly pheromones, which bring ticks together, and sex pheromones, that attract males to females and encourage growth. The life cycle of ixodid ticks is typically accomplished in 2–3 years, but it may take from 6 months to 6 years, varying with ecological circumstances (temperature, relative humidity, and photoperiod).

2.2.2. Host seeking

About 190% of Ixodid tick's life is spent unattached from their host (Hillyard, 1996), and most of them are living in open milieus, fields, or jungles (exophilic). Ticks are commonly active during specific seasons and looking for their hosts as ecological situations are very appropriate. Moreover, ticks are extremely alert to stimuli that reveal the occurrence of the hosts. These involve chemical stimuli, aromatic chemicals, humidity, and airborne atmospheres and body temperatures related to warm-blooded mammals. The exophilic ticks have two distinctive host-seeking performance forms. In the trap approach, ticks rise shrubbery and pause for moving hosts, with their front legs detained out in the same way as are insect probe. In the tracker approach, ticks attack hosts and appear from their environment and track toward their hosts when these animals appear close. Few tick species are host-specific, suckling on merely a narrow diversity of creatures. Some ticks have diverse hosts for each feeding stage, and host specificity may differ between the dissimilar phases in the same types.

2.2.3. Feeding and Attachment of ticks

The ticks may walk across on its host for numerous hours before feeding. It introduces only its hypostome into the skin, and numerous elements made by the salivary glands that enter the host during this penetration and producing a feeding pond (Boyce *et al.*, 1984; Francis 1929; Mangold *et al.*, 1998).. Throughout the earliest 24–36 h of attachment, the ingestion of blood is the absence or little, and the penetration and attachment are the main activity. The salivary excretions formed by ixodid ticks involved enzymes, a cement to anchor the mouthparts to the skin of the host, and anti-inflammatory, anti-hemostatic, vasodilators, and immunosuppressive substances. These enable effective blood-feeding, and an anesthetic in the saliva types the bite of ixodid

ticks commonly painless. The toxins in the saliva of some species may also cause paralysis of the host (Boyce *et al.*, 1984; Francis 1929; Mangold *et al.*, 1998). Ixodid ticks nourish for extensive periods, and 2–15 days are essential for a whole blood meal to be consumed, according to the feeding stage, species of tick, type of host, and site of attachment. An early sluggish feeding period (3–4 days) is followed by a period of fast distension (1–3 days) when ticks, mainly females, may increase their body weight up to 120- fold. While feeding, there are alternating stages of sucking blood and salivation, with vomiting happening regularly, at the end of the rapid engorgement stage. Throughout the early slow feeding stage, there is constant digestion of the blood meal in the midgut, and evacuation may occur. In the phase of rapid engorgement, there is reduction indigestion, but this develops and continuous after the tick is complete and detaches from the host. Ticks rapidly concentrate the blood meal by removing water and electrolytes in the feces, throughout transpiration, and in salivary gland secretions. Undigested deposits from the midgut and wastes from the excretory body are removed through the anus.

2.3. The Soft Ticks or Argasidae

The soft ticks or argasids are quite different from the ixodids. The argasids salivary glands do not make cement and comprise anticoagulant and cytolytic substances because the feeding only takes a short time (Boyce *et al.*, 1984; Francis 1929). Some larval stages, argasids may feed up to 10 times, develop and replete in a few hours. The coxal organs converge the blood meal, and the coxal fluid is discharged during and after the meal. The time spent on the host is relatively short, and after every meal, these ticks are classically originated in cracks and crevices in their habitats or just below the soil surface.

2.4. Tick's diseases

2.4.1. A Noninfectious Tickborne Disease: Tick Paralysis

Ticks can transmit many pathogens, but the prolonged attachment (5–7 days) of certain species of ticks may result in paralysis of the host (Francis 1929; Needham & Teel, 1991; Dworkin *et al.*, 1999). due to neurotoxic substances formed by the salivary glands of involved distended ticks (particularly females). Tick paralysis occurs globally, and it was firstly reported in Australia in 1824. There are more than 40 species of ticks from both families have been involved in the condition (Needham & Teel, 1991; Dworkin *et al.*, 1999). Tick paralysis happens more often in children, though adults may also be affected. The most important clinical signs include weakness in the lower extremities, which rises within hours or days to include the trunk musculature, upper extremities, and head. Patients may reveal ataxia or respiratory pain, and mortality rates of up to 10% have been reported (Examination of CSF samples commonly shows no irregularities, and the diagnosis of the condition varies with a history of tick bite or finding a tick on the body of the patient. Elimination of the tick can cause a rapid recovery within 24 hrs (Needham & Teel, 1991; Dworkin *et al.*, 1999).

2.4.2. Control

1. Reduction and controlling of tick populations are very challenging (79, 80). Milieu variations, involving vegetation management by cutting, burning, and herbicide treatment, and drainage of wet areas are one policy for tick control, but their effects are often short-lived, and they can cause severe ecological damage. In some areas, host exclusion or depopulation may result in a reduction in the density of ticks, but this is generally unreasonable and is also not environmentally rigorous.
2. The use of organophosphates or pyrethroids, which may be combined with pheromones to control ticks, may cause environmental contamination and toxicity for animals and humans, even when applied only to selected habitats. Acaricides, nevertheless, can be used directly to wild or domestic hosts to kill attached ticks and disturb tick nourishing.
3. Biological control methods for ticks are also existing, and these include the elevation of natural predators (including beetles, spiders, and ants), parasites (insects, mites, and nematodes), and bacterial pathogens of ticks; the mass discharge of males pasteurized by irradiation or hybridization; and the immunization of hosts against ticks (Felz *et al.*, 2000; Felz *et al.*, 1999; Jongejan & Uilenberg, 1994).
4. Recently, the control of ticks infestation is based on the perception of combined pest managing, in which different control methods are altered to one area or against one tick species with due consideration to their environmental effects.

2.4.3. Tickborne infectious diseases

A. Bacteria and ticks

Ticks may develop infected with bacteria by feeding on bacteremic animals or by transstadial and transovarial transmission. All kinds of spreading may occur for some bacteria; for example, the spotted fever group rickettsiae may transmit via all routes (Johnson *et al.*, 1984). Three facts are necessary to accept how bacteria are spread by ticks and the concerns for tickborne bacterial diseases. These are as the following:

1. Rickettsiae grow in almost all organs and fluids of ticks, in certain the salivary glands and ovaries, which allows diffusion of organisms during feeding and transovarially, respectively. Other bacteria may be transmitted transovarially but do not corrupt the salivary glands of their tick hosts and cannot then be transmitted to vulnerable vertebrate hosts where they might cause disease (Schmidtman, 1994; Niebylski, 1999).
2. Each phase of ixodid tick feeds only once, and bacteria gained by a tick during feeding can then be spread to another host only when the tick has sloughed to its next developmental phase. Not all species in a genus can

spread bacteria transstadially; such as, not all Ixodes species that requested *B. burgdorferi*, the agent of Lyme disease, transfer the agent transstadially and, consequently, act as vectors.

3. If the bacteria such as the rickettsiae are transmitted both transstadially and transovarially in a tick species, this tick will also be the reservoir of the bacteria, and the distribution of the disease caused by the bacteria will be identical to that of its tick host (Table 3). It is very unusual, but ticks may become infected with bacteria by co-feeding—that is, several ticks feeding nearby on the host—and, therefore, the direct spread of bacteria from an infected tick to an uninfected one might occur ((Johnson *et al.*, 1984). In only some rickettsiae and some species of relapsing fever, borreliae have a sexual transmission of bacteria from an infected male to female ticks been described (Johnson *et al.*, 1984). Scarce information is available about the significances of bacterial infections on the host ticks themselves, nonetheless lowered fertility and great mortality have been reported in ticks infected with *R. rickettsii* (Niebylski *et al.*, 1997). Also, it has yet to be recognized if the properties of bacteria, such as virulence, alter in the tick hosts. It is reported that *R. rickettsii* loses its virulence in guinea pigs when its host ticks are exposed to physiological pressure (Johnson *et al.*, 1984).

B. Tickborne zoonoses

The tick-transmitted bacterial diseases of humans that are presently known are zoonoses, with the bacteria being preserved in natural sequences, including ticks and wild and domestic animal hosts. The ticks may infrequently feed on people and thus cause infections. For each bacterial disease, one or numerous tick vectors and one or several reservoirs may occur (Currie, 2005). Animal hosts are liable to the bacteria and have to develop a moderately long period of bacteremia to be effective reservoirs of infection. The infectivity of the reservoir hosts, the tick infestation rate, and the host concentration are the main variables investigating the epidemiology of tick-borne diseases. These are manipulated by numerous biological and environmental elements (Currie, 2005), and which involve the inclination for the host of the diverse stages of ticks, degree of tick-host connection, periodical activities of equally ticks and host, the vulnerability of selected hosts to the bacteria, ecological circumstances, and host resistance. The percentage of ticks that gain bacterial infections may upsurge with the period of their attachment on the reservoir host, although feeding, as is the case with *B. burgdorferi* infections (Lane, 1994).

2.4.4. Transmission from ticks

Ticks spread bacteria to humans when their feeding sites are contaminated with infected salivary secretions such as *B. burgdorferi*, spotted fever cluster rickettsiae, relapsing fever borreliae; feces (*Coxiella burnetii*); or coxal fluid in the case of argasid ticks (some species of relapsing fever borreliae); regurgitated midgut substances (*B. burgdorferi*); The amplified danger of disease spread with increased attachment time has been confirmed for spotted fever group rickettsiae and *B. burgdorferi* (Johnson *et al.*, 1964). The indirect paths of spread are also possible, such as contamination of abraded skin or the eyes following the destroying of ticks by the fingers.

Ticks may fasten on people at various locations but are regularly located round the head and neck, and in the groin, however, some ticks favored the head and neck attachment sites such as *D. variabilis*, a vector of the Rocky mountain spotted fever; while *A. americanum*, a vector of human ehrlichiosis, attached mostly on the lower extremities and buttocks and in the groin; and *I. scapularis*, which transmits *B. burgdorferi*, attached at a wide variety of sites (Piesman *et al.*, 1991).

It is essential to observe that ixodids frequently do not produce pain while feeding, and immature phases are frequently not noticed on people because of their small size. The maximum occurrence of Mediterranean spotted fever happens in summer, the period while the immature phase of the vector is most prevalent (Johnson *et al.*, 1964). A record of a tick bite is then often not reported by persons who have the tickborne disease diagnosed (Johnson *et al.*, 1964). Tick-related factors that affect the degrees of infection in humans with tickborne bacterial diseases involve the occurrence of vector ticks and their infection rate, their willingness to feed on people, and the occurrence of their usual hosts. Human elements, like the probability of people entering the tick's biotope, the action of defeating ticks between fingers, and liability to the bacteria, also work a role. For example, the brown dog tick, *R. sanguineus*, is well modified to a human urban situation, where it is reasonably host-specific and infrequently feeds on people. *Amblyomma* species are the vectors of *Rickettsia africae*, in sub-Saharan Africa, and it is the agent of African tick bite fever. These ticks are frequently infected with the organism (150% in certain areas) and feed readily on people who enter their biotopes (the bush). The seroprevalence in people from these areas is, therefore, very high; it is often 180% (Johnson *et al.*, 1964).

2.4.5. Conclusion

Ticks are considered as the most important intermediate host for more than 15 new tickborne bacterial diseases that described globally. Several elements may clarify the amplified number of emerging tick-borne diseases or their amplified incidence. People's outdoor activities have resulted in exposure to ticks and tickborne pathogens. More actions need to improve awareness of tickborne diseases among primary care physicians, additional studies of potentially pathogenic bacteria originate in anthropophilic ticks, and application of molecular biology techniques have all significantly enabled studies of the epidemiology of emerging human tickborne diseases globally. Furthermore,

several *Rickettsia*, *Borrelia*, *Ehrlichia*, and even *Bartonella* species have been found in ticks only, and their pathogenicity in humans is yet to be investigated.

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The chemical composition and effect of *Chenopodium botrys* L. Chenopodiaceae on a mouse model of excisional wound: Introducing an herbal wound dressing

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Abstract

*This study was aimed to prepare pre-clinical evidences for wound dressing property of powder of *Chenopodium botrys* L. (Chenopodiaceae) on mouse model of excisional wound as reported in Kurdish ethnomedicine through*

millennia. Chemical composition of an essential oil isolated from aerial parts of *C. botrys* L. was analyzed by GC-MS. Eighteen male mice were randomly divided into three equal groups: the group receiving full wound dressing using powder (0.400 g), the group receiving partial wound dressing using powder (0.125 g) and the control group. From the first day of wound induction, the powder was daily dressed on the wounds of treated groups. The wound diameter was measured post-wounding daily and the healing process was evaluated and formulated. Among thirty-nine compounds of the essential oil of *C. botry* L. β -eudesmol (32.22%), elemol (23.35%), juniper-camphor (7.59%), cedren-9- α -ol (4.31%), α -santanol (3.76%) and myrcene (2.90%) were main *sesquiterpenes*. The wound closure rate showed the steepest in wounded mice received full wound dressing ($y = -1.8286x + 13.329$; $R^2 = 0.9244$) as compared to wounded mice received partial wound dressing ($y = -1.7048x + 12.671$; $R^2 = 0.9694$) and normal wounded mice which left to heal normally ($y = -1.5893x + 13.889$; $R^2 = 0.909$). However, there was not discrepancy among groups on the eighth post-wounding day which all wounds were repaired. The present study demonstrated that plant powder of *C. botrys* hastened the process of wound healing and shortened the time required for a complete wound healing.

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Keywords: *Chenopodium botrys* L., essential oil, GC-MS, wound closure rate, mice

Introduction

Chenopodium botrys L. Chenopodiaceae, is an annual or biennial herb has been used as expectorant, anticonvulsant and tonic remedy in Iranian traditional medicine (Zargari,

1993; Semnani and Semnani, 2015) while whole plant powder has been employed as herbal wound dressing in Kurdish ethnomedicine through millennia. The various extracts derived from *C. botrys* have been traditionally prescribed for catarrh and asthma, worm parasitism, pain, headache, common colds, and influenza (Semnani and Semnani, 2015). In Serbian traditional medicine, dried aerial parts of *C. botrys* were used as diuretic, antispasmodic, carminative, and antidiarrhoic remedies (Maksimović *et al.*, 2005). In Skardu valley of Pakistan, whole plant infusion is used orally for treatment of stomachache, liver complaints, and headache; it is also acknowledged as laxative and diuretic (Bano *et al.*, 2014). Young leaves and branches of *C. botrys* were used for healing of wounds in Kohistan valley, Khyber Pakhtunkhwa, Pakistan (Hazrat *et al.*, 2011).

In India, *C. botrys* is known as stimulant, diuretic, carminative, antispasmodic, and emmenagogue; it is also used in asthma, catarrh, and gastric and hepatic diseases (Semnani and Semnani, 2015). In Germany, *C. botrys* frequently cultivated against moths and used as a medicinal plant till nineteenth century (Semnani and Semnani, 2015). In Spain, *C. botrys* “Valladolid tea” prescribed for coughs and probably digestive disorders or wound infestation (Pardo *et al.*, 2005).

C. botrys of different origins yielded 0.08-2% essential oil (EO) containing flavonoids, alkaloids, and several terpenoids (Semnani and Semnani, 2015; Yousef *et al.*, 2011; Chitra *et al.*, 2009; Hosamani *et al.*, 2004; Schultz, 1999; Okoli *et al.*, 2007).

In this line, bicyclic sesquiterpenoids were found in *C. botrys* (Kokanova-Nedialkova *et al.*, 2009) and its distinguishing scent is caused by monoterpenes and sesquiterpenes (Kletter and Krichbaum, 2001). The headspace of *C. botrys* contained monoterpenes including camphor, δ -3-carene, fenchone, linalool, menthone, nerol, β -pinene, pulegone, terpineol-4 and thujone and sesquiterpenes including β -elemene, elemol and β -eudesmol (Hazrat *et al.*, 2011). Early studies on the EO of *C. botrys* mentioned to ascaridole as a bicyclic monoterpene with impressive biological activities (Kletter and Krichbaum, 2001). Iranian EO of *C. botrys* showed presence of 2,3-dehydro-4-Oxo- β -ionon, (+)-7-epi-amiteol, elemol, α -cadinol and *tau*-cadinol as main components (Mahboubi *et al.*, 2011). Moreover, in the EO of Greek *C. botrys*, sesquiterpenes including elemol acetate, elemol, botrydiol, α -chenopodiol, β -eudesmol and selina-3, 11-dien-6 α -ol have been identified as major components (Tzakou *et al.*, 2007).

Kurdish ethnics used the whole plant as a wound dressing. Hence, the aim of this study was to mimic precise traditional usage of whole plant powder of *C. botrys* in experimental wound healing to provide preclinical evidence for ethnic tradition of this plant as a wound dressing matter.

Materials and Methods

Essential oil of *Chenopodium botrys* L.

The samples of *C. botrys* have been collected from Bisotun (34° 23' N, 47° 26' E) region of Kermanshah province and authenticated by a botanist (second author). Seventy grams of dried herb was slightly crushed and emptied into the balloon of Clevenger apparatus to drain its EO. The EO of the plant was then completely thermo-extracted for 4 to 5 hours. At the end, the EO was extracted and completely dewatered and kept in the refrigerator for phytochemical analysis.

Gas chromatography–mass spectrometry (GC-MS)

Shimadzu model GC-17A (Kyoto, Japan) gas chromatograph coupled to a Shimadzu Quadruple-MS model QP5050 mass spectrometer was employed for GC-MS analysis. Compounds were separated on a 30 m × 0.22 mm i.d. fused-silica capillary column coated with 0.25 µm film of BP-5 (Shimadzu) and a split/splitless injector with a 1mm internal diameter glass liner. Ultra-pure helium was carrier gas with ionization voltage of 70 eV. Injector and interface temperatures were 280 and 260 °C, respectively. Mass ranged from 35 to 450 amu and program of oven temperature was the same as abovementioned for the GC. The constituents were identified using calculation of their retention indices under temperature-programmed conditions for *n*-alkanes (C8–C20) and the oil on a DB-5 column under the same chromatographic conditions. Genotype compounds was identified in comparison to their mass spectra with those of the internal reference mass spectra library (NIST08 and Wiley 9.0).

***In vivo* animal model of excisional wound**

Experimental design and animal maintenance were approved by ethical committee of Razi University and followed the NIH Guide for the Care and Use of Laboratory Animals. In this study, male Naval Medical Research Institute (NMRI) mice (*Mus musculus* L.; n = 18; six month-old; 20–25 g) were kept at 20 to 22 °C in 12 hours of darkness and 12 hours of light with free access to water and feed except during induction of wound. To wound, each animal was anesthetized with ketamine and xylazine cocktail and after preparation of the skin behind neck area, a circular excisional wound was made up with scissors in sterile conditions. The depth of the wound included dermis and hypodermis and the day of surgery was considered the first day. The diameter and duration of complete wound closure were measured. The wounded animals were randomly divided into three equal groups as follows: the group (P) receiving partial wound dressing by whole plant powder (0.125 g), the group (F) receiving full wound dressing by whole plant powder (0.400 g), and the control group (C) that did not receive any treatment. From the first day after the wound induction until complete recovery, the wounds in treated groups received *once-daily dressing* by whole *C. botrys*. The diameter of the wound was recorded and formulated daily till full wound closure presented by zero diameter (*vide infra*).

Statistical analysis

The SPSS version 22 software for Windows (SPSS, Chicago, IL, USA) was used to analyze the data. The wound area and the percentage of wound healing in different groups and in different days were analyzed by repeated measures ANOVA and *post hoc Tukey's HSD* was employed to compare the means. A P value ≤ 0.05 was considered as significant and results were reported as mean ± standard error of the mean (SEM).

Results

Essential oil of *Chenopodium botrys* L.

The chemical composition of EO isolated from *C. botrys* were presented in Table 1 and Figure 1. Accordingly, 39 compounds have been identified in the EO of *C. botrys*. The chief components were β-eudmesol (32.22%), elemol (23.35%), juniper-camphor (7.59%), cedren-9-α-ol (4.31%), α-santanol (3.76%) and myrcene (2.90%).

Figure 1. GC chromatogram of the EO extracted from *Chenopodium botrys* L. in Kermanshah, Iran. The x-axis shows the retention time (min), and the y-axis shows the intensity (abundance) of the signal.

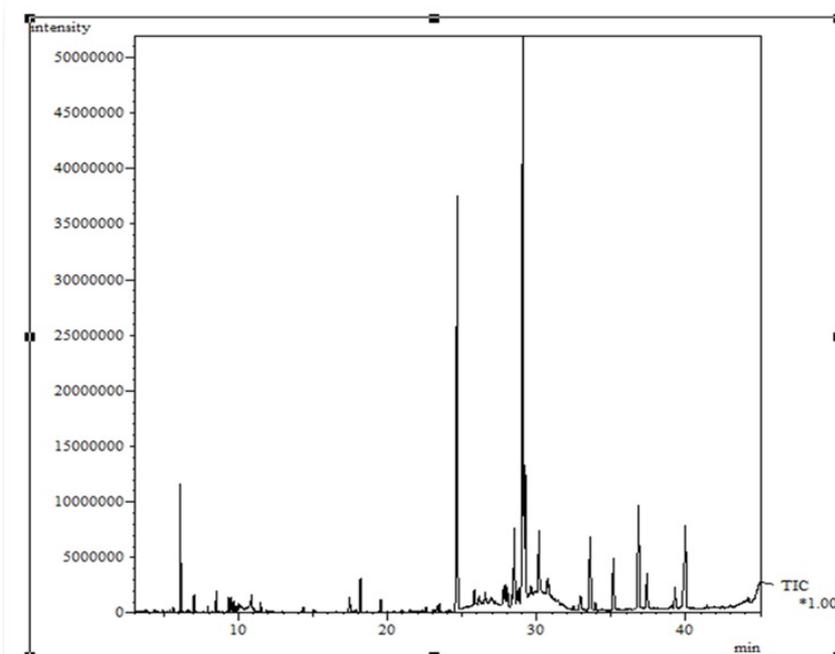


Table 1. Percentages of phytochemicals identified in essential oil of *Chenopodium botrys* L. in Kermanshah, Iran

| Compound | RT | RI | KI | Similarity | Area | Area% |
|-------------------------|--------|--------|------|------------|----------|----------|
| Hexanal | 3.767 | 801.6 | 800 | 88% | 458209 | 0.055597 |
| 2-Hexenal | 4.358 | 857.9 | 854 | 90% | 438150 | 0.055597 |
| α -Pinene | 5.367 | 937.8 | 939 | 90% | 427589 | 0.055597 |
| Camphene | 5.625 | 955 | 953 | 89% | 1084069 | 0.111193 |
| Sabinene | 5.967 | 977.8 | 976 | 88% | 477863 | 0.055597 |
| Myrcene | 6.1 | 990.3 | 991 | 94% | 26691673 | 2.909563 |
| 3-Carene | 6.608 | 1014.8 | 1011 | 90% | 998312 | 0.111193 |
| <i>p</i> -Cymene | 6.925 | 1030.0 | 1026 | 80% | 407004 | 0.037064 |
| Limonene | 7.008 | 1034.0 | 1031 | 95% | 4146566 | 0.444774 |
| Cineole | 7.133 | 1040.0 | 1033 | 80% | 410152 | 0.037064 |
| Terpinolene | 8.217 | 1092.1 | 1088 | 80% | 399552 | 0.037064 |
| Fenchone | 8.508 | 1104.5 | 1087 | 97% | 9533824 | 1.037806 |
| Cis- β -terpineol | 9.35 | 1134.7 | 1144 | 89% | 5116231 | 0.555967 |
| Pinan-2-ol | 9.508 | 1140.3 | 1142 | 93% | 4945540 | 0.537435 |
| Camphor | 10.217 | 1165.7 | 1143 | 80% | 2589124 | 0.277984 |
| Menthone | 10.283 | 1168.0 | 1154 | 80% | 647294 | 0.074129 |
| Isomenthol | 10.858 | 1188.6 | 1182 | 82% | 7889074 | 0.852483 |
| 1-Terpin-4-ol | 11.017 | 1194.3 | 1177 | 90% | 970656 | 0.111193 |
| α -Terpineol | 11.467 | 1208.6 | 1189 | 92% | 4293106 | 0.463306 |
| <i>trans</i> -Piperitol | 11.867 | 1220.3 | 1205 | 88% | 718583 | 0.074129 |
| Menthyl acetate | 14.342 | 1293.2 | 1275 | 91% | 2584668 | 0.277984 |

| | | | | | | |
|------------------------|--------|--------|------|-----|----------|----------|
| p-Menth-1-en-9-ol | 15.058 | 1312.8 | 1291 | 90% | 1308326 | 0.148258 |
| Terpinyl acetate | 16.55 | 1352.2 | 1350 | 88% | 618154 | 0.074129 |
| Undecanol | 17.433 | 1375.5 | 1372 | 97% | 7788017 | 0.852483 |
| β -Elemene | 18.167 | 1394.9 | 1391 | 90% | 14348685 | 1.575241 |
| Caryophyllene | 19.533 | 1429.7 | 1404 | 93% | 5494120 | 0.593032 |
| Germacrene D | 21.942 | 1490.9 | 1480 | 80% | 766905 | 0.092661 |
| β -Selinene | 22.558 | 1506.5 | 1485 | 87% | 2600952 | 0.277984 |
| δ -Cadinene | 23.308 | 1525.6 | 1524 | 88% | 2557690 | 0.277984 |
| Elemol | 24.667 | 1560.2 | 1549 | 90% | 13716039 | 23.35063 |
| Germacrene D-4-ol | 25.817 | 1589.4 | 1574 | 95% | 7948173 | 0.871016 |
| Caryophyllene oxide | 26.117 | 1597.1 | 1581 | 84% | 6927454 | 0.759822 |
| Guaiol | 26.542 | 1608.0 | 1595 | 94% | 10131909 | 1.111935 |
| Viridiflorol | 26.958 | 1618.8 | 1590 | 80% | 6158803 | 0.667161 |
| γ -Eudesmol | 28.025 | 1646.3 | 1630 | 91% | 9595564 | 1.056338 |
| Cedren-9- α -ol | 28.492 | 1658.4 | 1650 | 80% | 39488257 | 4.318013 |
| β -Eudesmol | 29.067 | 1673.3 | 1658 | 81% | 95404764 | 32.22758 |
| Juniper Camphor | 29.217 | 1677.1 | 1691 | 88% | 69634512 | 7.598221 |
| α -Santanol | 30.142 | 1701.0 | 1678 | 80% | 34397592 | 3.762046 |

Note: RI: retention index; KI: Kovats index; RT: retention time

The effect of *Chenopodium botrys* L. powder on skin wound healing in mice

On the first ($P_{ANOVA} = 0.989$; $F_{2, 14} = 0.011$), second ($P_{ANOVA} = 0.567$; $F_{2, 14} = 0.596$), and third ($P_{ANOVA} = 0.156$; $F_{2, 14} = 2.174$) day of the study, there were not any differences in the diameter of wounds among groups. However, in the 4th day of study, there was a significant difference in the diameter of wounds among groups ($P_{ANOVA} = 0.034$; $F_{2, 14} = 4.542$). In this day, both *C. botrys* treated groups showed similar wound diameters ($P = 0.228$) while diameter of wound closure was reduced significantly ($P = 0.028$) and non-significantly ($P = 0.448$) in P and F group compared to C group, respectively (Table 2). Also, in the 5th day of study, there was a significant difference among groups ($P_{ANOVA} = 0.002$; $F_{2, 14} = 10.541$). In this day, P ($P = 0.027$) and F ($P = 0.002$) group showed smaller wound diameters than that of C group (Table 2) while there was no difference in wound diameters between P and F groups ($P = 0.324$). On 6th day of the study, there was a significant difference in wound diameters among groups ($P_{ANOVA} = 0.02$; $F_{2, 14} = 5.540$). In this day, P ($P = 0.056$) and F ($P = 0.023$) group showed smaller wound diameters than that of C group (Table 2) while there was no significant difference between P and F groups ($P = 0.878$). On 7th day of the study, there was a significant difference in wound diameters among groups ($P_{ANOVA} = 0.018$; $F_{2, 14} = 5.714$) among groups. In this day, P ($P = 0.032$) and F ($P = 0.032$) showed a smaller wound diameter than C group but there was no significant difference between P and F groups ($P = 1.000$). Finally, there was no discrepancy among groups on 8th day of study and the wounds of all groups were completely resolved (Table 2).

Table 2. The wound dressing effect of *Chenopodium botrys* L. powder on the diameter of the skin wound (mm) in mouse model of excisional wound

| Group | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 |
|-------|----------|----------|---------|----------------------|----------------------|----------------------|---------|---------|
| C | 10.8±2.2 | 10.2±1.7 | 9.6±1.8 | 9.0±1.5 ^a | 7.8±0.8 ^a | 4.4±1.5 ^a | 2.0±1.8 | 0.0±0.0 |
| P | 11.0±2.7 | 9.0±2.0 | 7.6±1.1 | 6.6±1.1 ^b | 4.6±2.0 ^b | 1.2±2.6 ^b | 0.0±0.0 | 0.0±0.0 |
| F | 10.8±2.2 | 9.8±1.4 | 8.6±1.5 | 8.0±1.0 ^a | 3.0±1.8 ^b | 0.6±1.3 ^b | 0.0±0.0 | 0.0±0.0 |

NC: Control group, p: treated group with a low dose of plant powder (0.125 g), F: treated group with a high-dose plant powder (0.400 g). Values with different letters show significant difference at P value ≤ 0.05 .

The Figure 2 provided an overview of wound closure rate in all groups. It showed the reliable linear relations between wound diameter (y-axis) and time (day; x-axis) with similar wound diameter in initial day (y-intercept) and various slopes (closure rates). Based on various equations depicted in Figure 2, closure rate was the steepest (-1.8286) in F group among all groups and P group also showed more closure rate (-1.7048) than C group (-1.5893).

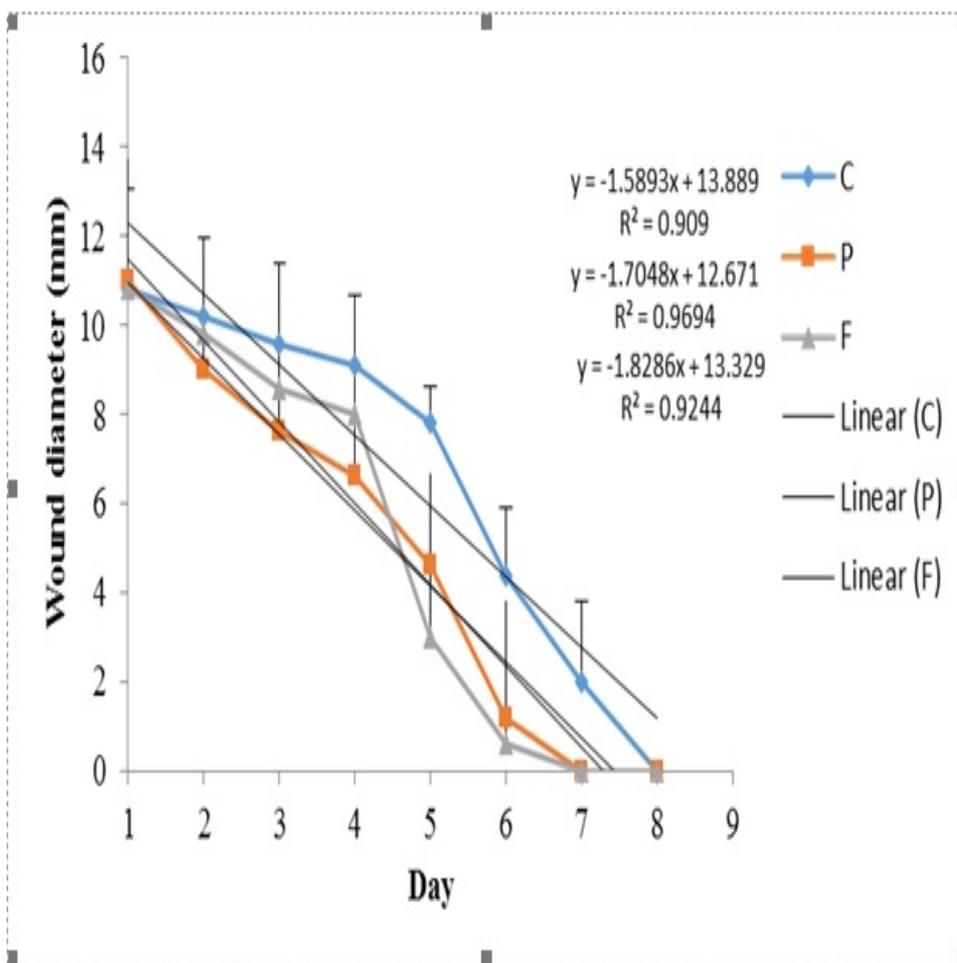


Figure 2. The effect of *Chenopodium botrys* L. powder on the closure of skin wound healing in mice.

(N = Control group, P = the treated group with low doses of plant powder (0.125 g), F = the treated group with High dose of powdered plant (0.400 g).

Discussion

Among compounds ($n = 39$) of EOs of *C. botrys*, β -eudmesol (32.22%), elemol (23.35%), juniper-camphor (7.59%), cedren-9- α -ol (4.31%), α -santanol (3.76%) and myrcene (2.90%) were detected as main components. In other study, the EO derived from aerial parts of *C. botrys* through hydro-distillation showed 29 compounds which α -oidmesol (15.2%), epi- α -morolol (11.1%) and cobenol (10.2%) were reported as major compounds (Rustaiyan *et al.*, 2003). In this continuum, the EO of this plant was extracted by hexane led to identification of 19 compounds which α -chenopodiol acetate (35%) and oidesmadien-6- α -ol (18.2%) were chief compounds (Rustaiyan *et al.*, 2003). The reason for the difference in the type and amount of phytochemicals in the EOs of *C. botrys* collected from different regions can be due to the various used parts of plants, and their different climatic and geographical conditions.

Several studies have been mentioned to essential oil or extracts of herbs as wound healers in traditional medicine, however the traditional application of herbs or parts of herbs have been not reported the strict applications of the extract or EO. The EO of *C. botrys* has been

studied widely and the presence of some oxygen-containing sesquiterpenes with prominent antibacterial and antifungal activities in various parts of this plant has been described (Kokanova-Nedialkova *et al.*, 2009; Yadav *et al.*, 2007; Tzakou *et al.*, 2007). For instance, the EO (0.43%w/w) isolated from aerial parts of *C. botrys* collected from southern Serbia exhibited significant bactericidal and fungicidal activity against an array of microorganisms like *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Aspergillus niger*, *Candida albicans*, *Sarcina lutea*, *Klebsiella pneumoniae*, *Salmonella enteritidis* and *Shigella flexneri* (Maksimović *et al.*, 2005). Moreover, the oil of *C. botrys* growing in Saudi Arabia showed antimicrobial activity (El-Sayed *et al.*, 1989). The results of antimicrobial activity of the EO from aerial parts of *C. botrys* growing in Greece were also reported (Tzakou *et al.*, 2007). The EO of *C. botrys* exhibited significant antibacterial activity against *Salmonella heidelberg* and *Bacillus cereus* and the residual water solution showed a good activity against *Salmonella heidelberg* and *Bacillus cereus* (Kokanova-Nedialkova *et al.*, 2009, Lyubenova *et al.*, 2006). The EO of *C. botrys* collected from suburb of Kashan, Iran showed strong antimicrobial activity against *Staphylococcus saprophyticus* followed by *Klebsiella pneumoniae*, *Bacillus cereus*, *Staphylococcus epidermidis*, *Streptococcus mutans*, *Listeria monocytogenes* and *Salmonella typhimurium* while this EO had minor effect on *Candida albicans* and showed inhibitory effect on *Aspergillus species* and *Bacillus subtilis* (El-Sayed *et al.*, 1989). More surprisingly, several species, including *C. botrys*, possess compounds that have been demonstrated to interfere with mitochondrial function (Semnani and Semnani, 2015). The wound area is very susceptible to infections caused by some abovementioned microorganism. Therefore, antimicrobial effects of various EOs derived from *C. botrys* may involve in accelerated healing process of wounds as compared to control animals. Wound is simply a loss of cellular and functional continuity of living tissue. Although the process of wound healing is natural (Chitra *et al.*, 2009.) as seen in control mice in this study, an infection can delay healing.

More specifically, one study showed that *C. botrys* L. EO improved wound healing activity in animals as a preclinical study (Sayyedrostami *et al.*, 2018). The obtained results showed that application of *C. botrys* L. on wounds induced considerable wound contraction and accelerated healing which is in agreement with the results of the present study, so it may be a good candidate to treat different types of wounds in animals and human beings (Sayyedrostami *et al.*, 2018). In contrast to Sayyedrostami *et al.*'s study (Sayyedrostami *et al.*, 2018), which focused on wound healing of *C. botrys* L. EO, we completely translated ethnical application of *C. botrys* whole plant as wound dressing material in a mouse model of excisional wound and our findings showed that the slope of wound closure were the steepest in wounded mice that received full wound dressing by *C. botrys* ($y = -1.8286x + 13.329$; $R^2 = 0.9244$) as compared to wounded mice that received partial wound dressing by *C. botrys* ($y = -1.7048x + 12.671$; $R^2 = 0.9694$) and normal wounded mice which left to heal naturally ($y = -1.5893x + 13.889$; $R^2 = 0.909$). The overview of previous investigations focused on wound healing potentials of selected *C. botrys* terpenoids have been summarized in seminal review (Rita *et al.*, 2013). In this line, numerous medicinal properties and phytochemicals like monoterpenes, sesquiterpenes and phenolic compounds have been reported in *C. botrys*. In this essence, β -eudesmol as a sesquiterpene was the most abundant chemical compound found in the EO of *C. botrys* which possesses many pharmacological effects including antitumor effects (Sghaier *et al.*, 2016), although its wound healing effect has not yet been reported. Among the other chemical compounds found in *C. botrys* EOs, one may mention to limonene, α -pinene, 3-carene, terpineol,

cineole, camphor, caryophyllene oxide and sabinene which are monoterpenoid compounds with anti-inflammatory effects (Rita *et al.*, 2013). In addition to anti-inflammatory properties, the properties of tissue repair have been reported for limonene (Rita *et al.*, 2013). Likewise, for terpineol, anti-cancer effects and wound healing have been reported (Rita *et al.*, 2013). Cineole has also been reported to be effective in the treatment of asthma and sinusitis. Caryophyllene oxide is also a monoterpene compound with anticancer and wound healing properties (Rita *et al.*, 2013). The α -santalol is also one of the many compounds in *C. botrys* EO which is a sesquiterpene effective in the treatment of skin diseases and skin cancer (Xiaoying *et al.*, 2010). Consequently, the EOs of *C. botrys* can be effectively applied in the treatment of various maladies like tissue injuries and wounds. In conclusion, the findings of this study not only prove the ethnical usage of *C. botrys* as a wound dressing remedy but also introduce a natural herbal wound dressing matter for traumatic conditions for desert dwelling inhabitants like Kurdish people. *It appears*, this wound dressing remedy initially dries wound area through osmosis because of its vascular texture and then sustainably release its antimicrobial or putative mitogenic compounds that speed up the wound healing process, however more investigations are acknowledged to decipher mechanisms of wound healing of *C. botrys*.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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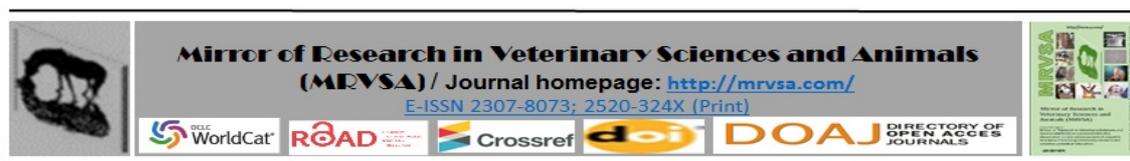
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Physiological effect and role of dietary folic acid in regenerative medicine: Review

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Abstract

Globally, there are several chronic and risk diseases like Alzheimer's, Parkinson's, coronary heart disease, high blood pressure, and congenital anomalies. Generally, the treatment of these diseases is very costly. However, many researchers

recognize the ways of their treatment by less cost with low potential toxicity. Researchers have been looked to the dietary sources and find the complex link between the food, especially the essential vitamins and the diseases. Folic acid or pteroylglutamic acid is active than a synthetic drug. Folic acid is one of the eight a water-soluble vitamins B. It is tremendously necessary for several activities in the body such as DNA synthesis, normal erythropoiesis with red blood cell maturation, inhibition of neural tube defects, depressing high homocysteine levels, nutritional regulation of the methionine cycle, reduce hematological indications, neurological, cancer diseases, and physiological condition of nutritional stress. Folate, vitamin B12, and vitamin B6 are working as a substrate in the methylation cycle. Using folic acid (folacin) supplement daily at a standard dose is essential to reduce the level of serum homocysteine. It is chiefly governing blood pressure, blood sugar, obesity, and control body weight. This review aims to study the applications of folic acid supplementation and its benefit to the body. Additionally, to recognize the improvements in lifestyles with using these supplements.

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Introduction

The structure of folic acid was not an active pattern. It can be converted to active form such as dihydrofolic and (reduced form) of tetrahydrofolic in the target liver organ (Bailey & Ayling, 2009). Folic acid is the oxidized form. It can be taken through diet since 1941. Folic acid belongs to the Latin term "foila," and it had been prepared synthetically from leaves of spinach plant (Beck, 2012). The chemical name of folic

acid is a pteroyl-glutamic acid. It is included in pteridine, para-aminobenzoic, and glutamic acid (Hazra & Tripathi, 2001). Folate is played a part in the transfer of a 1-carbon unit (methyl, methylene, and formyl unite) to the vital substrates, which comprises the synthesis of DNA, RNA, and proteins (Brocardo *et al.*, 2008). It is revealed a well-identified vitamin of the B-complex that soluble in water. Additionally, it plays a chief role in all mammals' actions (Choi & Mason, 2000). Moreover, folate has a great job at the therapeutic intervention level, with regenerative medicine plus neural engineering (Al-Mashhadane *et al.*, 2018). The leafy greens (Brussels sprouts), potatoes, broccoli, legumes, bread, white cereal products, dried beans, peas, and citrus fruits are the sources of folic acid in food (Dunlap *et al.*, 2011). The folic acid form is more bioavailable and stable than other shapes of folate (Ohrvik & Witthoft, 2011). In the methionine cycle, folate has precisely responsible for the conversion of homocysteine to methionine and production of the universal methyl donor S-adenosylmethionine (SAM) (Ganji & Kafai, 2006). Moreover, essential biochemical reactions are provided precursors for the synthesis of amino acids, purines, pyrimidines, methylation of DNA, and regular erythropoiesis (Zhao *et al.*, 2014). The collective supplements of folic acid and other vitamins have effected through pregnancy by given enough energy of metabolism and preventing child defects (Graulet *et al.*, 2007). Folate had a major effect in cows that had been amplified lactation performance and ruminal production (Lia *et al.*, 2016). In the first year of age, the serum folate levels were 60 % than at birth (Hay *et al.*, 2008). During pregnancy and lactation, the female body is needed a higher amount of folate that reached to a half (Erinç, 2018). Folate has a vital role in the central nervous system (CNS) (Reynold, 2006; Tettamanti *et al.*, 2006) with the enhancement of the nervous system and brain tasks of different ages (Schmidt *et al.*, 2012). Also, it might be acted as a preventive anti-teratogenic (Wentzel *et al.*, 2005). It could be a novel choice for patients, which suffered from a high average of homocysteine as a risk aspect for cardiovascular illnesses (Ansari *et al.*, 2009). Folate has been lowered the risk of cancers in certain tissues, the most notable in the colorectum (Choi & Mason, 2000), with a hepatoprotective agent (Woo *et al.*, 2006). Vitamins B groups are essentially working as a cofactor on the metabolism of homocysteine to methionine via the remethylation-process (Dominguezly *et al.*, 2010; Soares *et al.*, 2007). Folacin also revealed an important action in angiogenesis and vasculogenesis that occurred during the physiological process such as pregnancy (Williams *et al.*, 2011). Folic acid supplementation is recommended by physicians for patients with chronic kidney disease, especially for those under the hemodialysis, to prevent nutritional deficiency and to facilitate hematopoiesis (Bravo-Soto *et al.*, 2016). Taking a special amount of folic acid might be prevented several malformations involving problems in craniofacial clefts, heart, limbs, and others (Cieřlik & Cieřlik, 2018).

Folate deficiency

Nutritional folate deficiency is one of the most significant dietary health problems worldwide (Ganji *et al.*, 2006). It leads to an imbalance and impairs DNA replication with damage in chromosomes due to incorrect access of DNA uracil that uses in cell division and tissues such as bone marrow (Duthie1999; Kawakita *et al.*, 2018). The low level of folate is the cause of different abnormalities in the newly born like neural tube defects, megaloblastic anemia, abruption placentae, spontaneous abortion, and congenital heart defects (WHO, 2015). It is also responsible for impair fertility

(Laanpere *et al.*, 2010) and slowed tumor growth in rat mammary compared with other animals (Sie *et al.*, 2009). Studies showed that the diminished folate had been alternated with choline and acetylcholine metabolism in young rats. It has a larger effect on the peripheral nervous system than on the brain that leads to abnormalities of synaptic function in model animals (Crivello *et al.*, 2010; Shea & Chan, 2008; Serra *et al.*, 2008). The effects of folic acid supplementation on central nervous system growth processes are not restricted only to the embryonic period. However, it can also be useful for enhancing growth and repair in the later phases of pregnancy and during lactation (Iskandar *et al.*, 2004). Elevated homocysteine levels due to folate deficiencies were associated with cell death and DNA damage. Also, the defects of hemoglobin include sickle cell anemia and Thalassemia that could be explaining in these cases (Rabaneda *et al.*, 2008; Sati'Abbas *et al.*, 2011). In some conditions, the correction of folate deficiency or additional supplementation may be beneficial, while in other conditions, it may be unfavorable (Branda *et al.*, 1998).

Megaloblastic anemia can be due to folate or vitamin B12 deficiency. Because the two vitamins share a metabolic pathway, treating a vitamin B12 deficient patient with folic acid will resolve the megaloblastic anemia but not resolve neurological damage due to vitamin B12 deficiency. It is the basis for the concern over 'masking' vitamin B12 lowering (Crider *et al.*, 2011). Folic acid increases the risk of cancer in cell and animal tissues (Krokan *et al.*, 2017). It has an excellent antioxidant property (Quang, 2018) as well as, other researchers were showed a high level of the weights of animals like ewes and lambs who were dealing with folic acid (Suhdoon *et al.*, 2009). It is highly sensitive to several environmental factors such as heat, UV light, and oxygen and related to hazard dropping folic acid in the blood (Thomas *et al.*, 2002). The folic acid is the active form of vitamin B9 with top choice is absorbed without needing any bio alteration (Patel & Bhaumik, 2019). Also, it acts as a first-carbon carrier, and vitamin B12 acts as co-factor for the enzyme methionine synthase (Mahajan *et al.*, 2019). Methotrexate and pemetrexed are done most prescribed anti-folates, and these are mainly treated with acute myeloid leukemia, osteosarcoma, and lung cancers (Samodelov *et al.*, 2019).

Increased of folic acid

In early reports were observed, the increase of folic acid intake might delay the diagnosis of vitamin B-12 deficiency. However, the higher folate intake may be decreased the risk of Alzheimer's disease independent of other risk factors, mainly vitamins B6 and B12 (Luchsinger *et al.*, 2007). The higher doses of folate are the possible masking of cobalamin deficiency in pernicious anemia (Sahay & Hen., 2007). As well as neurogenesis by neurological mask signs (Kadziela *et al.*, 2003) also profoundly damage of prostate cancer (Tester, 2014).

Dosage of folic acid

Folic acid is recommended at 400 micrograms, for healthcare and avoidance from genetic malformations (neural tube defects) for three months before conception and during the first trimester of female pregnancy (Hashmi *et al.*, 2018).

Using folic acid supplement 0.4 mg daily is essential to reduce the level of serum homocysteine, especially in hypertensive, diabetic patients, to decrease the risk of

cardiovascular events and to controlling blood pressure, blood sugar, and obesity (El-Maghraby *et al.*, 2016). Continuously used vitamin B supplementation did not decrease the danger of emerging type II diabetes (Song *et al.*, 2009). Folate availability is important acted during the first few weeks of pregnancy, and that reduces the risk of newborn defects (Niculescu & Zeisel, 2002). The super dose of folic acid was initiated by acute kidney damage (Bravo-Soto & Madrid, 2016). Daily folate intake of 200–320 µg appeared to be associated with a lower risk of breast cancer (Zhang *et al.*, 2014). Obeid & Herrmann, (2012) found that dose, 5mg of folic acid supplementation lead to high weight mass in animals fed a high-fat diet.

Folic acid effective

Aghamohammadi *et al.*, (2011) has been determined the pharmacological doses of folate. They found that folate supplementation lowered plasma homocysteine in patients with type II diabetes mellitus. Depression is associated with elevated cortisol levels (Stetler & Miller, 2011). On the other hand, Folates were operated as an antidepressant without a co-current pharmacological mediator (Brocardo *et al.*, 2008). The combination treatment between betaine and folic acid was more effective in lowering serum homocysteine than treatment by either alone (Kamel, 2010). When vitamin B-12 status was normal, however, high serum folate was associated with protection against cognitive impairment (Morris *et al.*, 2007.)

Diminished phagocytosis process and bactericidal of neutrophils are caused by folate deficiency (Stanger, 2002). Folic acid had become biofunctional in carcinogenesis (Rashedi *et al.*, 2018). At the same time, it is considered as an anti-oxidants agent in along of life (Rathor *et al.*, 2015). Dietary supplements of folic acid did not affect reproduction variables such as ovulation rate, fertility, and mortality rate (Méthot *et al.*, 2008).

Folate is absorbed in about 50% efficiency, while folic acid is absorbed in 85%-95% efficiency (Bailey, 2004). The molecule of folic acid effect by different types of solutions like Dimethylsulphoxid, Acetic Acid, Ethanol, and others (Attaf & Hasan, 2019). An anti-folate drug is called Pemetrexed (MTA) that use for lung cancer treatment (Yang *et al.*, 2013). The folates were more sensitive to technologic processes, mainly UV, ions (copper, iron), and chiefly heating exposure in a long period, all these factors reduce the quantity of this vitamin (Kapka *et al.*, 2012). The anemia and other diseases of blood might be resulted by deficiencies of zinc, vitamin B12, and folate (Guralnik *et al.*, 2004). Therefore vitamins B 12 are the most effective factor in preventing oxidative reactions (Lee *et al.*, 2015).

Folic acid relationship with Homocysteine

Homocysteine is a midway structure of methionine degradation; it is usually methylated to methionine. However, the process of catalyzed by the methionine synthase needs a metabolite of folate as a methyl donor and a metabolite of vitamin B12 as a substrate (Rezvani& Rosenblatt, 2008). Homocysteine is metabolized by remethylation or transsulfuration (De la Calle *et al.*, 2003). Hyperhomocysteinemia results from genetic defects in the enzymes or nutritional deficiencies in vitamin cofactors (Zhang *et al.*, 2004). Folic acid is absorbed into the bloodstream by the intestines, then converted to other

forms of folate by the liver. However, there is no evidence of harmful effects of metabolized folic acid in the blood of infants (Kawakita *et al.*, 2018). All the results were revealed that rat liver folate metabolism represents a typical case of the modular organization of cellular metabolism with several separate metabolic systems (Mitra *et al.*, 2013). Metabolites of the 5-MTHF and folic acid metabolic cycle -contribute to the formation of purine rings and the conversion of uracil to thymidine for DNA creation (Scott *et al.*, 2000). High cortisol levels were negatively associated with serum folate levels and positively associated with serum homocysteine levels (Casalheira *et al.*, 2008).

Conclusion

This review showed that folate-targeted liposomes that can promote enhanced drug uptake by the diseased cells, also profoundly reduce the collateral normal tissue toxicity like in cancer and inflammatory diseases. Moreover, folic acid has doubled actions in carcinogenesis depended on the dose and biological conditions of folic acid. Therefore, more studies were founded as the main place on the surface of cells as folate receptors. Also, folic acid can be used for diagnosis and treatment of cancer in non- invasive diagnosis methods. More studies found a poor association between dietary folate and lung cancer. Likewise, High dietary folate intake was associated with pointedly decreased damage to breast cancer. Cancer cells are more needed of this vitamin than other cells, It is prevented the progression of pre-existing tumors. Folate plays a dual role in cancers. It protects against the initiation of cancer but also aids in the growth and progression of pre-neoplasms and subclinical cancers. More studies found there was no association between total folate and many types of tumors like lung, gastric, oesophageal, breast, prostate and ovarian cancer if presented there is restricted evidence which suggests folate protects against these cancer danger . Many types of research and reports about the relationship between folic acid and diseases especially cancer had been effected or non-effected in low or normal doses of folic acid as well as the target tissue, age of the patient, family history and genetic factors, all these factors contributed of the main job of these vitamins. The original case for dietary folic acid is reducing the incidence of neural tube defects and folic acid a good option as anti hyperhomocysteinemia and lipid-lowering.

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Conflicts of interest

The author declares no conflict of interest.

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