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RESEARCH ARTICLE

EXPLORING THE MEDICINAL MARVEL: THE POTENTIAL OFYARSAGUMBA AS REGENERATIVE MEDICINE AND IN WOUND HEALING

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Abstract

Yarsagumba(Cordyceps mushroom) a valued herbal medicine, is a fungus that grows on ghost moth larvae. It belongs to the Ophiocordycipitaceae family and has been used in traditional Chinese medicine for centuries. It has various applications in the pharmaceutical and health industries. In Nepal, Yarsagumba has been recognized for thousands of years and is considered one of the most promising medicinal mushrooms. Scientists have been studying its unique life cycle and medical uses for the past 30 years.However, once correctly identified, these enigmatic organisms hold great promise in the prevention and treatment of numerous ailments such as cancer,woundhealing, antidiabetic, alleviating fatigue, respiratoryproblems, and erectile dysfunction in men.Cordyceps fungi possess significant phytochemicals, namely cordycepin and adenosine, which function by suppressing the adenosine A2 receptor and consequently inhibiting various neuroinflammatory markers such as NF-κB, NLRP3 inflammasome, IL-1β, iNOS, COX-2, TNF-α, and HMGB1. Yarsagumba's wound healing properties are multifaceted, with its anti-inflammatory and antioxidant compounds reducing inflammation and preventing tissue damage. Its immunomodulatory effects enhance the body's immune response and inhibit the growth of harmful microorganisms, reducing the risk of infection. Yarsagumba's regenerative capabilities stimulate collagen production and promote angiogenesis, resulting in improved wound healing outcomes and minimized scarring. This review examines how Yarsagumba's bioactive compounds can enhance wound healing, reduce scarring, and improve tissue repair. It also explores the plant's regenerative properties, such as its ability to stimulate stem cell growth and differentiation. Our findings indicate that the activation of adenosine receptors by adenosine and cordycepin effectively triggers the Wnt/β-catenin signaling, which can potentially facilitate tissue remodeling and serve as a therapeutic approach for skin wound treatment.

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Introduction:-

Nature serves as a remarkable symbol of symbiosis, showcasing its exceptional phenomenon. In addition to the fundamental essentials of life, namely food, clothing, and shelter, nature generously offers a comprehensive repository of remedies to heal all human ailments (1). The field of medicine has made significant progress today, thanks to advancements in science and technology. Despite these impressive developments, only a third of the 30,000 known human diseases or disorders can be treated symptomatically with existing drugs. Additionally, this treatment method carries a significant economic and social burden (2).

Nature is the main source of many important pharmaceuticals, providing a wide range of drugs derived from traditional systems and folklore practices in India. Medicinal plants are particularly important in the Traditional System of Medicine and are increasingly used to treat common diseases and nutritional disorders. However, there are also other sources of medicinal value beyond plants and herbs. Fungus, for example, has been found to have medicinal properties and the potential to produce new compounds with medicinal benefits. Researchers have conducted extensive studies on fungus to explore its medicinal potential (3-7).

One such fungus is Cordyceps sinensis popularly known as Yarsagumba, a valued herbal medicine and therapeutic biofactory, is a combination of fungus and dead insect that grows on ghost moth larvae. “Yarsagumba” widely recognized in Tibetan and Nepalese languages, is a valuable commodity traded in numerous nations. This unique item consists of an intact single piece containing both the caterpillar and fungal components. (8). It belongs to the Ophiocordycipitaceae family. Yarsagumba, an annual, non-chlorophyllous fungus also belonging to the ergot family, is an extremely rare species. It is primarily found in the alpine region of the Himalayas, at elevations exceeding 4000m. This fungus grows in various districts of Nepal, particularly above the snowline in Dolpa, Jumla, Humla, Kalikot, Baglung, Mustang, Manang, and Rasuwa. In Jumla district, it is mainly confined to areas such as Patarasi, Chhumchaur, Dillichaur, and Patmara. Additionally, Yarsagumba can be found in Tibet, North-East India (specifically Himachal Pradesh and Uttarakhand Himalayas), China, and Bhutan (9-10).

Yarsagumba is harvested prior to the monsoon season and upon its complete emergence from the larva, which occurs from April to August. Subsequently, it undergoes a drying process and is utilized in medicinal applications. Over the past few years, the global average temperature has risen by 0.85^{o}C from 1880-2012 and is projected to increase by a minimum of 0.3^{o}C–1.7^{o}C (RCP 2.6) to a maximum of 2.6^{o}C–4.8^{o}C (RCP 8.5) by the end of this century. In terms of the Chinese caterpillar fungus habitat, approximately 6.02% (8,989 km^{2}) of the Nepal Himalaya is currently suitable. However, all future climate change trajectories over three different time periods indicate an expansion of the predicted suitable habitat of Chinese caterpillar fungus, with an expansion of 0.11–4.87% over the current suitable habitat (11-12). Scientists have been studying its unique life cycle and medical uses for the past 30 years. Yarsagumba (Mushrooms) have long been utilized as a food source in forests, yet their potential for therapeutic purposes remains largely untapped due to limited awareness and knowledge. However, once correctly identified, these enigmatic organisms hold great promise in the prevention and treatment of numerous ailments such as cancer, and wound healing. Yarsagumba's wound healing properties are multifaceted, with its anti-inflammatory and antioxidant compounds reducing inflammation and preventing tissue damage. Its immunomodulatory effects enhance the body's immune response and inhibit the growth of harmful microorganisms, reducing the risk of infection.

Yarsagumba's regenerative capabilities stimulate collagen production and promote angiogenesis, resulting in improved wound healing outcomes and minimized scarring. Further research is needed to fully explore Yarsagumba's potential in wound healing, but its multifaceted approach makes it a promising natural remedy for enhancing wound healing processes and improving patient outcomes.Yarsagumba enhances overall health and well-being. It aids in body detoxification and enhances immunity, thereby reducing the risk of various diseases. It offers benefits to the heart, lungs, reproductive organs, brain, and blood vessels. Additionally, it promotes improved blood circulation, oxygen absorption, stamina, and endurance. Consequently, it has gained popularity among athletes who utilize it to enhance their performance. Despite its effectiveness, Cordyceps supplements are quite costly; however, they are available in the form of extract capsules, powder capsules, liquid extracts, and tablets (13).

Name and General Description:

Cordyceps sinensis, also known as cordyceps mushroom and caterpillar fungus, is an ascomycetes fungus that belongs to the family Clavicipitaceae. The name Cordyceps is derived from the Latin word’s 'cord' and 'ceps', which signify 'club' and 'head', respectively. These terms solely depict the physical characteristics of the fungus (14).

The Chinese refer to it as 'Hiatsao tong tchong' and 'dong chongxiacao', while in Tibetan it is known as 'Yartshagumba', 'Yarsagumba', or 'Yartsagunbu', which translates to 'winter-worm summer-grass'. This peculiar organism transforms from a worm in winter to a type of 'grass' in the summer. In the Himalayan regions of India and Nepal, it is referred to as Keera ghaas, which means 'insect herb' (14-16).

Cordyceps, commonly referred to as the Chinese caterpillar fungus, is a parasitic organism that thrives on a rare caterpillar known as Hepialisarmoricanus. This peculiar fungus grows on the caterpillar until it perishes, eventually giving rise to a mushroom that emerges from the caterpillar's head. While the term 'Cordyceps' typically denotes the species C. sinensis, it is worth noting that numerous species within the Cordyceps genus have been documented worldwide (14,17,18).

Fig1:- Dried Cordyceps sinensis.

Vernacular & Names Synonyms (13)

Well-Know with Names	Yarsagumba& Cordyceps Sinensis
Botanical Synonym	Cordyceps Sinensis
Botanical Name	Ophiocordyceps Sinensis
English Name	Caterpillar Fungus, Caterpillar Mushroom, Chinese Caterpillar Fungus
Tibetan Name	Yarsagumba
Chinese Names	Dong Chong Xia Cao, Tochukaso, Tung Chung Hsia Tsao
Others	CS-4, Champignon Chenille, Vegetable Caterpillar,

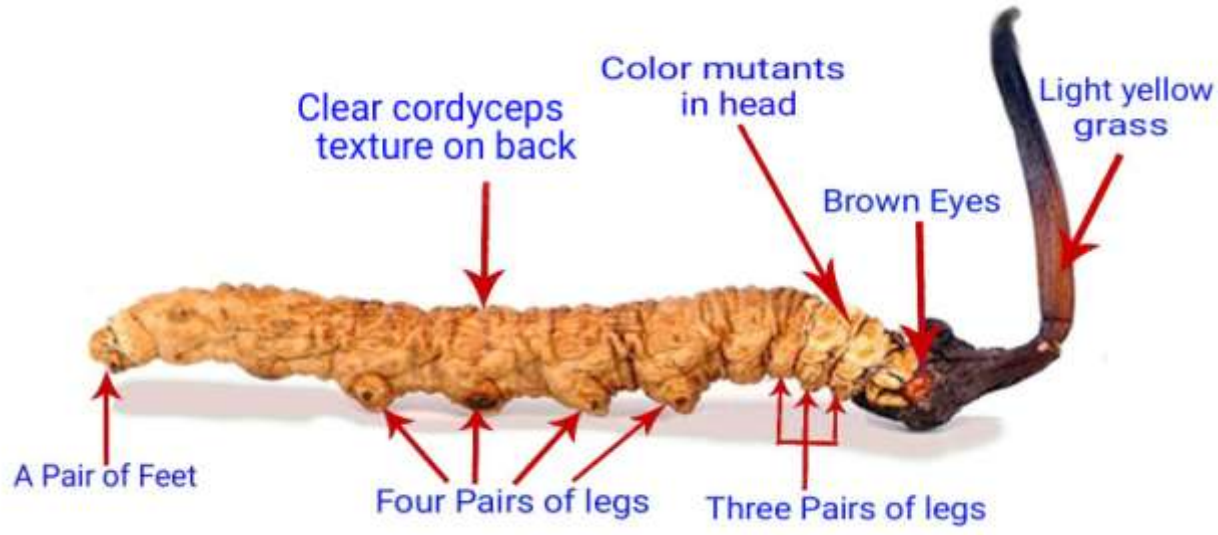
Mycobiota data of Yarsagumba

Kingdom: Fungi
Phylum: Ascomycota
Family: Clavicipataceae
Species: C. sinensis (Berk.) Sacc.
Genus: Cordyceps
Order: Hypocreales
Class: Ascomycetes

Structure

Yarsagumba is composed of two parts: a dead caterpillar at the lower part and a fungus at the upper part. The fungus features a small spike with dark brown fructification and a yellowish-white stalk. Its size ranges from 4 to 12 cm in length and 0.14 to 0.4 cm in girth. Yarsagumba, when both the caterpillar and fungal parts remain intact in a single piece, is traded as a commodity. This particular species is not cultivated in Nepal; however, it is being cultivated in America by growing the strain on soybeans for medicinal purposes. Yarsagumba has been a significant component in traditional medicine worldwide for many years due to its medicinal effects. However, due to the constantly increasing demand and the challenges in harvesting, Yarsagumba has become the most expensive medicinal substance globally (19,20). The primary chemical constituents of O. sinensis include proteins and nitrogenous compounds, polysaccharides and sugar derivatives, sterols, nucleosides, phenolics, fatty acids, and vitamins (21). This potent and natural fungal herb is known for its effectiveness in preventing and treating wounds and various diseases, such as asthma, chronic bronchitis, tuberculosis, cardiovascular diseases including hypertension, kidney problems, acute and chronic hepatitis, and various types of tumors (22).

Fig-2:- Outer structure of Yarsagumba.



History

Around 1500 years ago, Cordyceps, a type of fungus, was first discovered in Tibet. It caught the attention of Nepalese and Tibetan herders who noticed that the yaks and goats grazing in the high mountain pasture would exhibit strange behavior after consuming this peculiar substance. These animals would become lively and engage in playful activities, driven by a strong desire. As a result, the local inhabitants who consumed Yarsagumba, the name given to this fungus, also experienced a surge in vitality. The earliest recorded mention of Yarsagumba can be attributed to Nyamnyi Dorje, a Tibetan physician and lama who lived between 1439 and 1475. In his work titled "An Ocean of Aphrodisiacal Qualities," he provides detailed information about the mushroom's significance as a sexual tonic (23).

Approximately 1000 years later, the physicians of the Ming Dynasty's Emperor discovered this remarkable Tibetan marvel and combined it with their own knowledge to create a potent and effective medicine. During the Qing Dynasty in 1757, Cordyceps was initially utilized as a medicinal remedy in China. Its current global renown and demand surged in 1993 when numerous Chinese long-distance runners achieved world records. In 1843, a British mycologist named Berkely first designated it as Sphaeria sinensis Berk. Later, in 1878, Saccardo renamed it Cordyceps sinensis. Cordyceps sinensis (Berk) Sacc. is the scientific term for the final stage of the fungus, which is the fruiting body that emerges from a deceased caterpillar? Previously known as Cordyceps sinensis, the fungus underwent a name change in 2007 due to molecular analysis, resulting in the creation of the Ophiocordycipitaceae

family and the transfer of several Cordyceps species to Ophiocordyceps. Consequently, Ophiocordyceps sinensis is an alternative name for Cordyceps sinensis. Cordyceps militaris (L.) Link (the most commonly used alternative), Cordyceps hawkesii Gray, Cordyceps martialis Speg, Cordyceps liangshanensis Zang, C. hawkesii Gray, C. hawkesii Gray, C. hawkesii Gray, C. hawkesii Gray, Cordyceps nepalensis, C. hawke, Cordyceps sinensis, Cordyceps nutansand, and C. hawkesii Gray are the three Cordyceps species reported in Nepal. Primarily, Cordyceps sinensis has been employed for medicinal purposes among them (24). The caterpillar fungus yarsagumba has predominantly been used as an immune-boosting tonic in traditional Chinese medicine. Modern pharmacological investigations have revealed its extensive range of pharmacological and therapeutic effects on various diseases, including renal, respiratory, liver, cardiovascular, and nervous system ailments. Additionally, it has been found to possess anti-cancer, anti-tumor, anti-viral, cholesterol-reducing, immuno-modulating, and antioxidant properties.Yarsagumba is well-known for its capacity to enhance stamina and libido (25). Ophiocordyceps sinensis was extensively used during the 2003 outbreak of the SARS virus (Severe Acute Respiratory Syndrome Virus) in China (26).

Life cycle

During the summer and early fall, Yarsagumba fruiting bodies release ascospores into the air, which infect and germinate inside ghost moth larvae. As the larvae shed their skin (27), the fungal cells spread throughout their bodies via the circulatory system. Due to their subterranean nature, the larvae dig further into the soil and enter from the back in a vertical position. This results in the Yarsagumba host larvae remaining upright, with the herb developing from their heads. Throughout the winter, the fungal cells rapidly develop inside the larvae, consuming all of their internal organs except for the exoskeleton. These fungal cells then transform into endosclerotium, a compact white mass within the larvae's bodies. The endosclerotium is a dormant stage in the Yarsagumba's life cycle that can withstand unfavorable climatic conditions, particularly cold temperatures. When spring arrives and the outside temperature gradually rises, the endosclerotium germinates and emerges through the prothorax region of the head, eventually reaching the soil.

The portion of Yarsagumba that emerges from the host larva is known as the stroma. A mature stroma consists of a stalk, stipe, or stem at the base, and a head, or fertile section, at the apex. During the summer, the stroma reaches complete maturity, and the fertile section of the head produces ascospores. These ascospores infect larvae in the surrounding area. This is the time of year when collectors begin to gather Yarsagumba. Consequently, the life cycle of Yarsagumba takes one year to complete. It starts by developing from the host larva and forms a mushroom-fruiting body above ground in the spring and summer. In the autumn and winter, it grows inside the host larva (28,29).

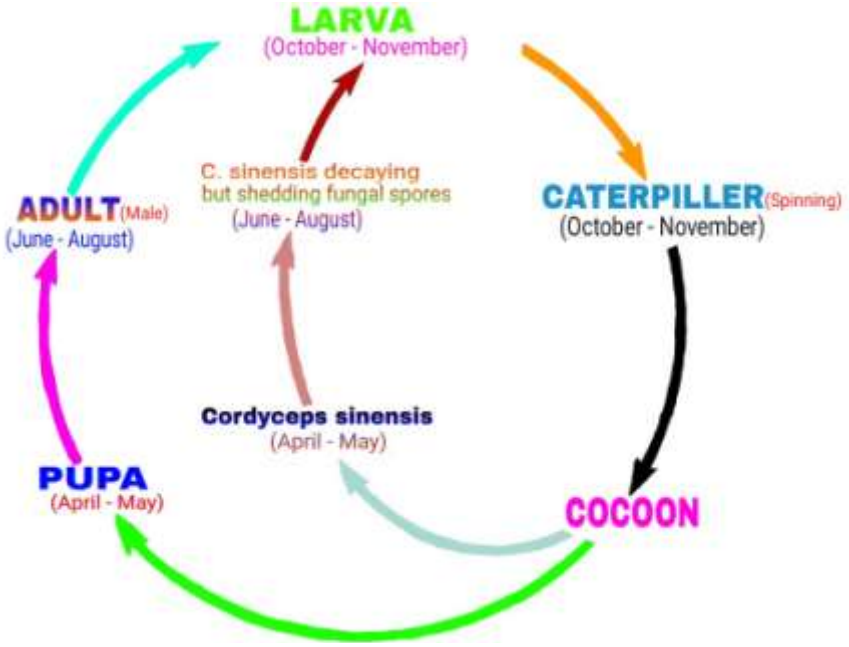


Fig 3:-Life cycle of Yarsagumba.

Figure 4:- stages of caterpillar fungus.

Regeneration

Natural regeneration occurs when the spores of the fungus initiate the growth process. During the onset of the monsoon season, the spores attack the caterpillar shortly after it emerges from its cocoon. If the fungus is collected early in the monsoon, the caterpillar can still be observed alive. However, if the collection takes place later in the monsoon, the caterpillar will no longer be alive. Following the melting of the snow, the fungal component of this species can be observed growing out of the ground, while the caterpillar part remains buried beneath the soil. It is worth noting that this particular species is not cultivated in Nepal. However, Yarshagumba is being cultivated in America by growing the strain on soybeans for medicinal purposes (30).

Morphology:

The fruit body of the organism is dark brown to black in color, while the larval body which acts as the "root" and contains the mushroom's mycelium, is yellowish to brown. It measures 5-15 cm in length and 0.14 to 0.4 cm in thickness. In the market, there are two available variants distinguished by their color. The larger variant has a whitish yellow color and is of higher quality. On the other hand, the smaller copper-colored variant is compromised in terms of both size and quality (31,32).

Distribution:

It is typically found in high altitude regions that range from 3,600 to 4,200 meters above sea level. Its presence has been documented in various locations, including the Nepal Himalaya, Tibet, Bhutan, Sichun, Qunghai, Xizang, and Yunnan provinces of China. In India, it is primarily located in the elevated regions of Kumaun Himalaya and Garhwal Himalaya, as well as in the higher altitudes of Arunanchal Pradesh and Sikkim (33).

Traditional Use of Yarsagumba

The caterpillar fungus, which has been used in Traditional Chinese Medicine for over 2000 years, is well-known for its ability to improve stamina and fertility, strengthen the respiratory and kidney systems, treat cancer and asthma, and most notably, cure impotence and increase sexual desire. Because of these effects, it has earned the nickname "Himalayan Viagra." According to a Tibetan medical manuscript from the 15th century, this fungus is considered a valuable remedy as it can eliminate prana ailments, treat bile disorders, and does not cause an increase in phlegm. Additionally, it specifically enhances sperm production.

After the 1993 World Championships in Athletics, the coach of a group of highly talented Chinese female distance runners disclosed that his athletes had consumed a combination of yarsagumba and turtle blood. These runners subsequently achieved world record-breaking performances, which resulted in a notable surge in the demand for the tonic. Ecologist Daniel Winkler, who has extensively studied the fungus, states in one of his research papers that yarsagumba has now become a symbol of social status and a prestigious gift among the affluent and influential in China, akin to French champagne.

Phytochemistry and Pharmacology

Yarsagumba has shown effectiveness in treating various conditions including wound healing, hyposexuality, arrhythmias, night sweats, hyperglycemia, hyperlipidemia, as well as heart, respiratory, renal, and liver diseases. The natural Cordyceps contains chemical constituents such as amino acids, cordycepic acid, glutamic acid, polyamines, cyclic dipeptides, saccharides, sugar derivatives, sterols, nucleotides, nucleosides, 28 saturated and unsaturated fatty acids, fatty acid derivatives, other organic acids, vitamins, and inorganic elements. The main components of both natural and cultured Cordyceps are palmitic acid, oleic acid, stearic acid, linoleic acid, and ergo sterol (34).

Nucleosides, such as cordycepin, have been identified as the primary active components of yarsagumba. These nucleosides have demonstrated significant efficacy in the treatment of cancer and viral infections. To enhance their therapeutic potential, various derivatives of nucleosides have been developed as anticancer and antiviral agents. Cordyceps Sinensis, in particular, contains a wide range of pharmacologically active nucleosides and their derivatives, including adenosine, adenine, inosine, cytosine, cytidine, uridine, guanine, uracil, thymidine, guanosine, and hypoxanthine. These nucleosides have also been utilized as biomarkers for quality control purposes in C. sinensis. Cordycepin, specifically, has been reported to possess neuroprotective properties, making it beneficial in the management of focal cerebral ischemic or reperfusion injury (35). Furthermore, cordycepin has demonstrated oral activity in the treatment of myocardial infarction. Numerous reports have also highlighted the immune-regulating, analgesic, broad-spectrum antibacterial, antiviral, and insecticidal activities of Cordycepin (36). Another important nucleoside, adenosine, exhibits various activities including energy transfer, signal transduction in cells, cytoprotection, prevention of tissue damage, anti-inflammatory effects, and anticonvulsant properties. Adenosine monophosphate (AMP) serves as a precursor to adenosine in C. sinensis, which is further converted into inosine through oxidative deamination (37).

Several biologically active compounds have been extracted from C. sinensis, including three nucleotides (adenosine-5-monophosphate, uridine-5′-monophosphate, and guanosine-5′-monophosphate) that have been shown to boost the immune response, influence fatty acid metabolism, promote iron absorption, and repair gastrointestinal injury (38). Additionally, a variety of intracellular and extracellular polysaccharides have been isolated, with monosaccharide composition analysis revealing the presence of ribose, rhamnose, arabinose, mannose, xylose, glucose, mannitol, galactose, sorbose, and fructose (39). Experimental studies have demonstrated a range of pharmacological actions, including free-radical scavenging, anti-tumor, immunoprotection, anti-influenza virus, hypocholesterolemic, and hypoglycemic effects (40). Notably, an exocellular heteropolysaccharide has been identified for its immunomodulatory and antitumor activities, while an acidic polysaccharide composed of galactose, mannose, and glucose has been found to possess cytoprotective effects against hydrogen-peroxide-induced injury in PC_{12} cells (40).CPS-1, a water-soluble glucomannogalactan polysaccharide, exhibits potential antioxidant activity that is beneficial for managing blood glucose levels and renal failure (41).

CPS-2, another polysaccharide, inhibits the proliferation of human mesangial cells induced by platelet-derived growth factor BB. Additionally, a non-ionic branched mannoglucan with a molar mass of 7.7×10^3 Da demonstrates weak cytotoxicity against SPC-I cancer cell-line. Furthermore, CME-1, a polysaccharide found in C. sinensis mycelia, protects RAW264.7 cells from oxidative stress by inhibiting S Mase activity and reducing C_{16} and C_{18} ceramide levels (42).

Cordyglucans, CS-F10, and cordysinocan are substances found in mycelium that have been studied for their strong effects against tumors, ability to lower blood sugar levels, and enhancement of phagocytosis, respectively. Acid phosphatase, on the other hand, is an enzyme that exhibits enzymatic activity. C. sinensis, a type of fungus, contains various sterols such as ergosterol and H1-A. Ergosterol is a precursor of Vitamin D, while H1-A has been linked to autoimmune disease (43). Other important sterols and glycosidic derivatives found in C. sinensis include ergosteryl-3-O-β-D-glucopyranoside, 22,23-dihydroergosteryl-3-O-β-D-glucopyranoside, 5α,8α-epidioxy-24(R)-

methylcholesta-6,22-dien-3β-D-glucopyranoside, and 5,6α-epoxy-24(R)-methylcholesta-7,22-dien-3β-ol. The latter two have shown potential as anticancer agents. Fungi also contain a wide range of protease enzymes, both inside and outside the cells. Additionally, a unique acid deoxyribonuclease that remains active in acidic conditions without the presence of divalent ions has been isolated from cultured C. sinensis (44). Furthermore, a new enzyme called serine protease, which has fibrinolytic activity, has been reported. The amino acid and polypeptide composition of C. sinensis includes cordymin, cordycedipeptide-A (3-acetamino-6-isobutyl-2,5-dioxopiperazine), cordyceamides A and B, tryptophan, and glutamic acid. Cordycedipeptide-A has been found to have cytotoxic effects on L-929, A375, and Hela cell-lines (45).

Chemical composition of yarsagumba

S.NO.	Constituents	Chemical Compounds	Nutritional functions
1.	*1)* Nucleotides and Nucleosides	*2)* Adenine, uracil, uridine, guanine, guanosine, thymidine, and deoxy uridine and cordycepin	Cellular metabolism relies heavily on their presence and they have been associated with enhanced immune function and overall well-being (50).
2.	Organic Acid	Palmitic, linoleic, cordycepic acid and stearic acids.	Consuming it in moderation can potentially provide health benefits by enhancing nutrient absorption (48).
3.	Sterols	Ergosterol, delta-3 ergosterol, ergosterol peroxide, - 3-sistosterol, daucosterol and campasterol.	*3)* Potential benefits for skin health, management of cholesterol, and potential possession of antiinflammatory properties are present (46).
4.	Nitrogenous compounds	Guanosine, Thymidine, Uracil, Tridine, Dideoxyuridine, Guanine, Inosine	*4)* They function as an antioxidant and aid in the prevention of harm caused by active oxygen species (47).
5.	Amino Acid	Proline, valine Phenylalanine, histidine, arginine oxyvaline.	*5)* To regulating various physiological processes, they also play a vital role in the development and repair of tissues in the body (49).
6.	Saccharides and sugar derivatives	Polysaccharides, d-mannitol and oligosaccharides	A source of energy is provided by them
7.	Phenolic acid	Vanillic acid, p-hydroxybenzoic acid	Their possession of antioxidant characteristics is acknowledged (47).
8.	Cyclic dipeptides	*6)* cyclo-(leu-pro), cyclo-(thr-	*7)* They possess properties that

		leu), cyclo-(gly-pro), cyclo- (ala-leu) and cyclo-(ala-val	are recognized for their immunomodulatory, antioxidant, and antitumor effects (50).

Skin Wound healing

A wound refers to a disruption in the continuity of bodily tissue caused by external force, which includes actions such as surgery. Numerous classifications can be made within this broad definition, considering the different types of violence or tissue damage.

The primary differentiation lies between open and closed wounds. Open wounds occur when the protective surface of the body, such as the skin or mucous membranes, is breached, allowing foreign substances to enter the tissues. In contrast, closed wounds do not expose the damaged tissues to the external environment, enabling the repair process to occur without the complications of contamination to varying degrees. Additionally, further categorizations can be established based on the manner in which the wound is produced.

Types of wounds

Open wounds

When the skin or mucous membrane is broken, foreign material such as bacteria, dirt, and clothing fragments can invade the wounded tissues, leading to potential complications from infection. Additionally, if the break in the skin is large, the drying and cooling effects of the air can exacerbate the damage caused by the wounding agent. While a needle or sharp knife may cause minimal damage, irregular and jagged objects like bomb fragments can produce extensive damage in all directions. Crushing injuries also frequently result in serious harm.

The skin possesses a remarkable ability to withstand injury due to its robust and flexible nature, as well as its rich blood supply, which facilitates rapid recovery. Conversely, the subcutaneous fatty tissues are more vulnerable to damage and are easily deprived of their blood supply. Muscle tissue is also susceptible to harm from shrapnel, as it is prone to tearing and cannot survive with reduced blood flow for an extended period. In the event of muscle damage, the risk of infection is particularly high. When it comes to open wounds involving bone, any detached fragments that lose their blood supply due to infection will remain in the wound as foreign bodies, leading to further complications. Even if the bone is cleanly broken and there are no loose fragments, infection can still enter the raw surfaces of the fracture, resulting in disastrous consequences.

Closed wounds

The severity of injury resulting from a direct impact depends on the force and direction of the impact. It is clear that as the force increases, the damage becomes more severe. The direction of the impact is equally important, although it may not be recognized as readily. For example, a blow to the side of the head with a hammer can cause severe bruising on the scalp, but if the force is directed slightly differently, it can cause extensive damage to the base of the skull. Other factors such as anatomy and physiology can also affect the extent of injury. Therefore, a fall on an outstretched hand can have different effects on a child, a young adult, and an elderly person.

Even a minor impact can cause harm to the skin and underlying soft tissues. This is evident through bruising or contusion, which occurs when small blood vessels rupture and blood infiltrates the tissues, as well as swelling caused by fluid passing through damaged capillary walls. Typically, the bleeding stops abruptly and within a few days, the blood and fluid are absorbed, leading to the affected area returning to its normal state. However, when larger blood vessels are damaged, a larger amount of blood escapes and accumulates in the tissues, forming a mass called a hematoma.

Any of the underlying tissues, such as blood vessels, nerves, muscles, bones, joints, or internal organs, can be affected by a forceful blow. The impact can cause damage to deeper tissues either directly or through the transmission of force to a weaker point in the body. For example, a blow to the hand may result in injuries to the flesh and bones of the hand itself, but it is common for a break to occur at a different location in the arm where the force is transmitted. The specific breaking point is determined by the direction of force and the individual's anatomy (51).

General Mechanism of Skin Wound Healing

The process of skin wound healing is a captivating mechanism that provides an evolutionary advantage not only to mammals but also to other species. The healing of skin wounds is a crucial step for survival as it serves as a physical, chemical, and bacterial barrier. Despite extensive research on wound healing mechanisms, there are still many unanswered questions. The physiological regulation of skin wound healing is a complex process that involves multiple cell types and mediators interacting in a highly sophisticated temporal sequence. Although certain interactions during the healing process are critical, redundancy is high, and other cells or mediators can adopt functions or signaling without significant complications. The aim of this update on skin wound healing is to focus on the various phases involved in the process. wherein hemostasis, inflammation, proliferation, and the eventual formation of mature scar tissue play integral roles (52).

Hemostasis

After an injury, hemostasis begins immediately, involving vascular constriction, platelet thrombus formation, coagulation cascade propagation, clotting termination, and fibrinolysis for clot removal to control bleeding (53). When the vascular endothelium is damaged, blood flows to the wound site, exposing the basal lamina. Activated platelets adhere to the exposed collagen, triggering the release of growth factors, inflammatory mediators, and cytokines, initiating intrinsic and extrinsic coagulation pathways, forming a fibrin clot to prevent further blood loss (54). Additionally, cytokines released during hemostasis play a crucial role in extracellular matrix deposition, chemotaxis, epithelialization, and angiogenesis, including transforming growth factor-beta, platelet-derived growth factor, fibroblast growth factor, epidermal growth factor, and vascular endothelial growth factor (53).

Inflammation

After an injury, inflammatory cells move to the site of the wound once platelets are activated. Mast cells assist in this movement by releasing vasoactive cytokines, such as prostaglandins and histamine. These cytokines increase the permeability of capillaries and promote local dilation, which helps with the migration process.

Initially, neutrophils are the main inflammatory cells attracted to the wound area due to bacterial products. They engulf bacteria and dead tissue, leading to the formation of pus within 48 to 72 hours after the injury. Later on, monocytes transform into macrophages and further clean the wound by removing the matrix and other debris like fibrin and spent neutrophils. Macrophages have a crucial role in releasing inflammatory cytokines like transforming growth factor-beta, platelet-derived growth factor, fibroblast growth factor, and epidermal growth factor. These cytokines are necessary for successful wound healing, and any hindrance in macrophage function can cause delays in the healing process (53, 54).

Overall, the inflammatory phase creates a sterile wound area, which serves as the basis for subsequent repair mechanisms.

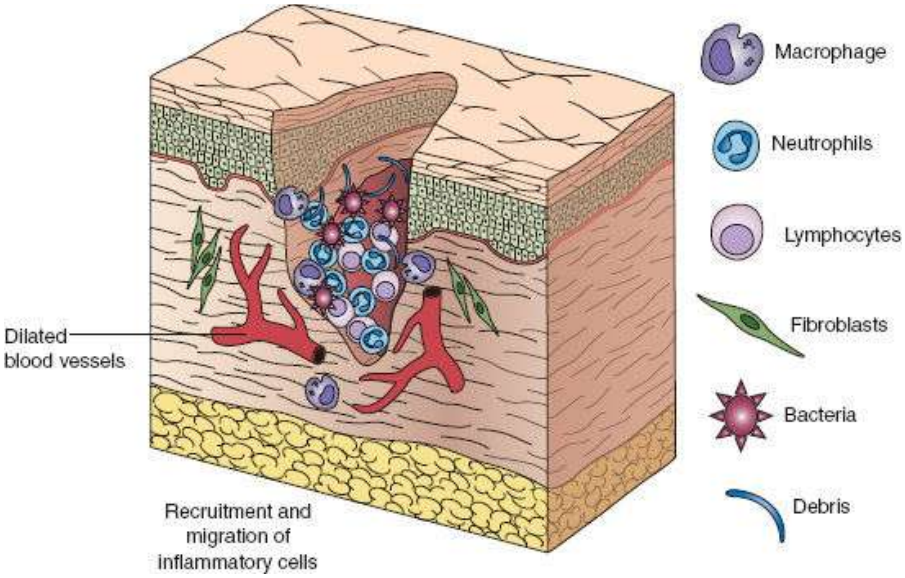


Fig5:- Phase 2- inflammation (59).

Proliferation

During the proliferative phase, which occurs between 3 to 21 days after injury, various processes take place such as angiogenesis, collagen deposition, granulation tissue production, and epithelialization. The primary objective of this phase is to fill the wound defect. Endothelial cells synthesize nitric oxide (NO) due to hypoxic conditions in the wound bed, which stimulates the release of vascular endothelial growth factor and promotes angiogenesis. Additionally, the release of fibroblast growth factor and platelet-derived growth factor also triggers angiogenesis, which supplies the new wound with oxygen, glucose, and other necessary factors for proper healing. Thin-walled endothelium branch from preexisting vessels and lay their foundation on the newly synthesized extracellular matrix. As blood flow returns to the area, oxygen saturation normalizes, and NO levels along with vascular endothelial growth factor decrease to slow the process of angiogenesis. This autoregulatory mechanism plays a role in preventing excess collagen production and abnormal scar formation. Migrating fibroblasts synthesize elastin and collagen to form the new extracellular matrix necessary for vascular support and granulation tissue. Granulation tissue is a highly vascular connective tissue and is essential to the final stages of wound healing, maturation, and remodeling.

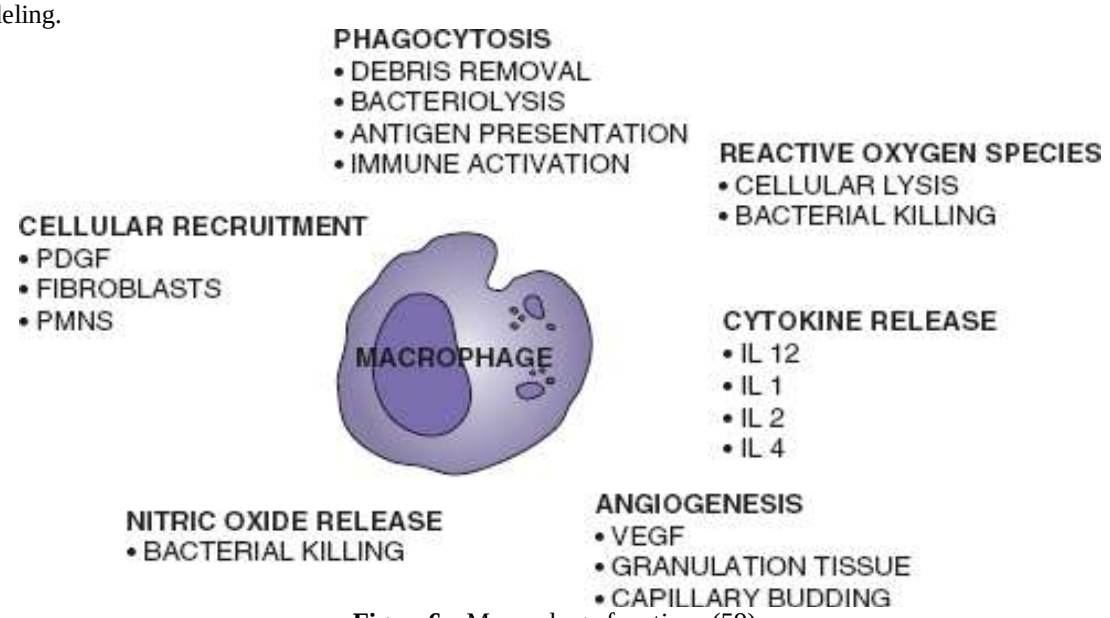


Figure6:- Macrophage functions (59).

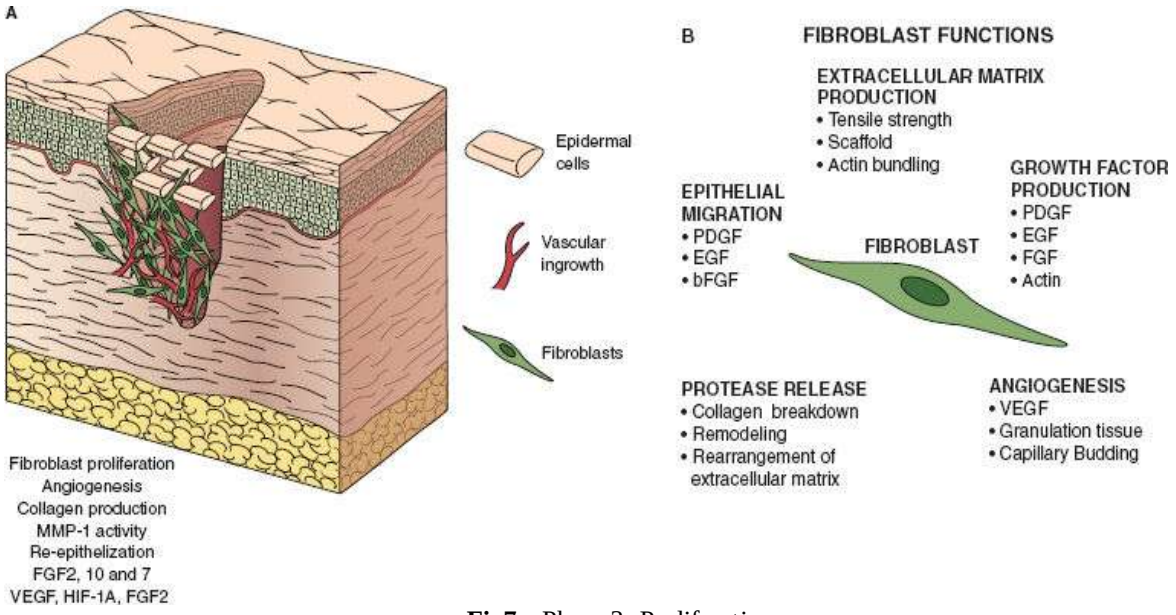


Fig7:- Phase 3- Proliferation.

Vast array of cells is recruited into the wound bed and carry out diverse functions including proliferation and deposition of ECM. **B:** Fibroblast functions **(59).**

Maturation

During the final stage of wound healing, known as the maturation phase, collagen cross-linking and remodeling take place, along with wound contraction. Fibroblasts initially synthesize type 3 collagen, which is thinner than the mature type 1 collagen found in healthy skin. As the maturation phase progresses, type 1 collagen replaces type 3 collagen in the granulation tissue, resulting in scar formation and increased wound strength. However, a wound can only regain 80% of its original strength three months after injury, and full restoration of pre-injury strength is impossible (53). Wound contraction occurs with the help of myofibroblasts and alpha-smooth muscle actin synthesis (55), and the mobility of surrounding tissue affects the success of contraction. Epithelial cells migrate inward from the wound edges to form a new protective layer, with varying migration rates allowing for stratification and tissue depth restoration. Once healed, scars are firm, slightly raised, and red due to excess collagen deposition and increased vascularity, but will eventually soften, flatten, and become paler over time (56, 57).

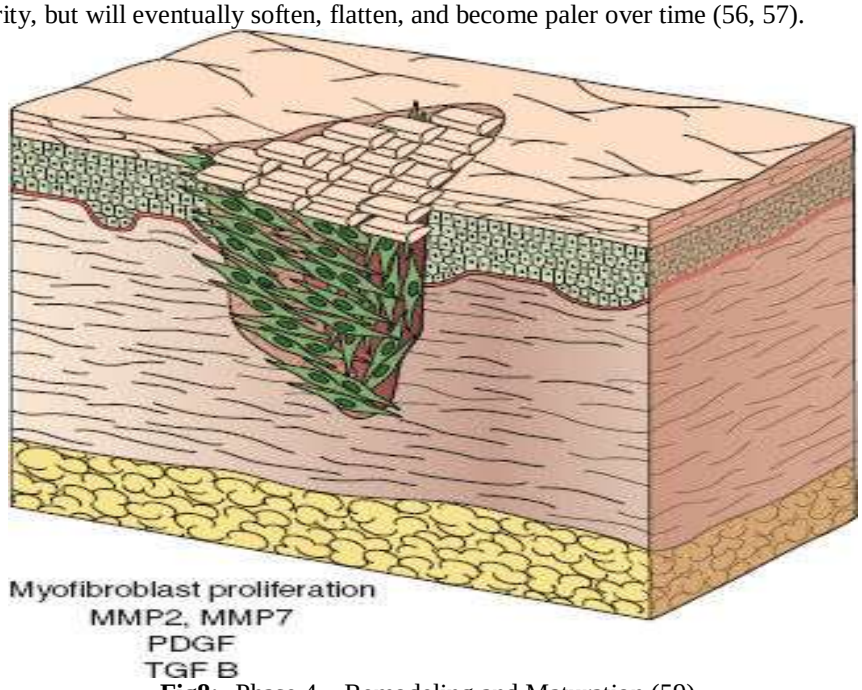


Fig8:- Phase 4 – Remodeling and Maturation (59).

Pathophysiology

Keloids and hypertrophic scars can sometimes form as a result of an exaggerated healing response. Hypertrophic scars stay within the original wound area, while keloids extend beyond it. Factors such as joint movement, underlying bone structures, and tissue loss can influence the development of these scars. People with darker skin are more prone to keloids.The exact process of scar formation is still not fully understood. However, keloids have been found to have abnormal or hyperactive fibroblasts. These fibroblasts produce excessive amounts of collagen, elastin, fibronectin, and proteoglycan, and respond excessively to stimulation. This is likely due to the increased presence of insulin-like growth factor receptors on keloid fibroblasts, which stimulates collagen production. Unlike normal scars, collagen in keloids is arranged in a disorganized manner, causing them to extend beyond the wound edges.

On the other hand, collagen in hypertrophic scars is bundled and arranged in wavy patterns parallel to the surface of the skin. This organized pattern sets hypertrophic scars apart from the chaotic arrangement seen in keloids.

Fibroblasts in hypertrophic scars respond normally to growth factors and produce only a slight excess of collagen. Additionally, hypertrophic scars contain unique nodular structures of alpha-smooth muscle actin myofibroblasts, similar to those involved in scar contraction. It is believed that over time, hypertrophic scars may diminish, while keloids will not (58).

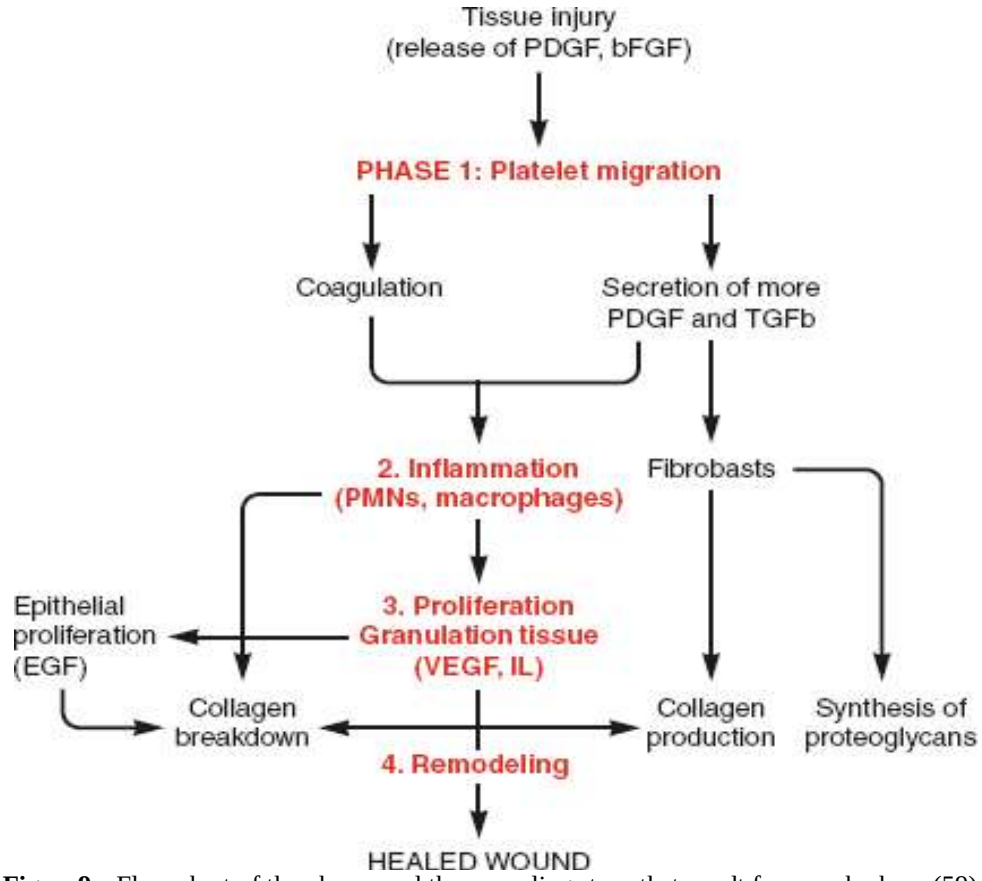


Figure9:- Flow chart of the phases and the cascading steps that result from each phase (59).

Yarsagumba use as a Wound Healing and regenerative Potency

Yarsagumba is a parasitic fungus that grows on the larvae of the Himalayan bat moth. It is a rare and valuable commodity, with a high demand in traditional medicine and the international market. The fungus is known for its aphrodisiac properties, which have earned it the nickname "Himalayan Viagra." It is also believed to have anti-inflammatory, antioxidant, and immune-boosting effects. In traditional medicine, yarsagumba has been used to treat a wide range of ailments, including respiratory disorders, kidney problems, and fatigue. It is also believed to have wound-healing properties, with some studies suggesting that it can accelerate the healing process and reduce inflammation. One of how yarsagumba may promote wound healing is by stimulating the production of collagen, a protein that is essential for the formation of new tissue. It may also help to increase blood flow to the affected area, which can speed up the delivery of nutrients and oxygen to the wound site (60).

The chemical constitution of yarsagumba which are used to prevent the various types of wounds and having regenerative potency to restore the damage tissue and put new organs tissue together.

Chemical Constituents

The Cordyceps Sinensis's chemical makeup promising to prevent and treat various type of wounds.

Nucleosides

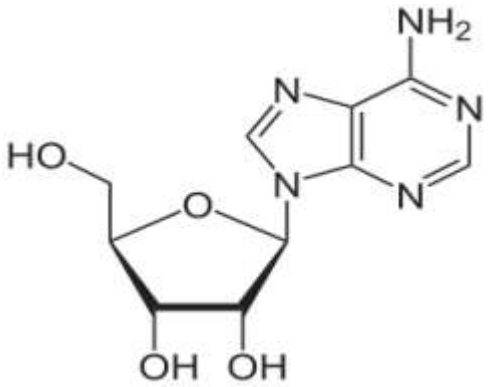
Cordyceps Sinensis comprises a significant proportion of nucleosides, which serve as crucial components. Additionally, nucleosides are a valuable indicator for evaluating the excellence of the caterpillar fungi (61).

The following nucleosides derived from the C. Sinensis have been extracted.

1. ADENOSINE
2. ADENINE
3. CYTIDINE
4. CORDYCEPIN

5. CYTOSINE
6. HYPOXANTHINE
7. GUANINE
8. GUANOSINE
9. INOSINE
10. 3-DEOXYADENOSINE
11. URACIL
12. THYMIDINE
13. URIDINE

Adenosine



Adenosine, a powerful endogenous physiological agent, governs a diverse range of physiological functions. Its physiological impacts are brought about by its interaction with any of the four identified cell-surface receptors (A1, A2A, A2B, and A3).The healing of full thickness dermal wounds can be enhanced through the topical application of adenosine A1 or A2A receptor agonists, although the specific adenosine receptors involved and the underlying mechanism for this effect have yet to be fully determined (62, 63). Among the various pharmacological properties that may contribute to its wound-healing effect, adenosine has been reported to exhibit angiogenic properties based on in vitro studies. In vitro, adenosine, acting at A2 receptors, promotes endothelial cell migration, proliferation, and the secretion of vascular endothelial growth factor (64-74). Furthermore, adenosine has been shown to be angiogenic in the chorioallantoic membrane angiogenesis assay and is prominently present at the periphery of developing vasculature during retinal vasculogenesis and oxygen-induced retinopathy in vivo, where adenosine A2A and A2B receptors and 5'-nucleotidase are highly expressed (74-78).

Role of Adenosine in Fibrosis

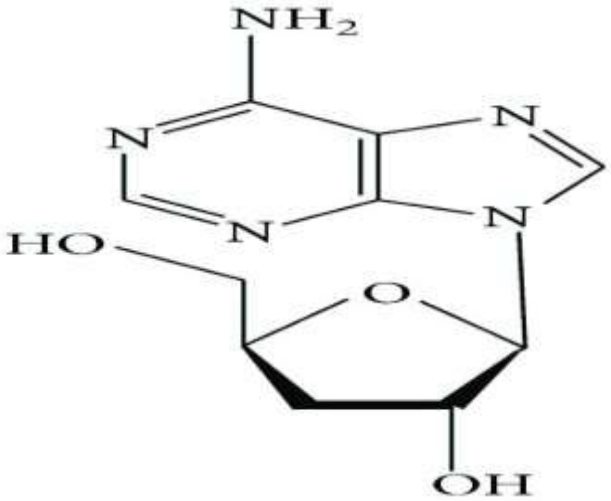
The process of fibrosis, which is a mechanism for healing wounds, involves a series of stages including hemostasis, inflammation, and structural repair. The coordination of these phases is carefully regulated by immune cells, epidermal cells, and dermal fibroblasts (79).

A_{2A} Adenosine Receptor Agonists Promote Wound Healing

Recent reports have indicated that the application of an A2AAR agonist topically accelerates the rate of wound closure (80). The involvement of A2AARs in this pharmacological effect was demonstrated by the observation that the specific A2AAR antagonist reversed the effect of the selective A2AAR agonist CGS21680 on wound healing, while antagonists targeting other ARs did not. In vitro treatment of wounds with this AR agonist stimulated fibroblast migration, and in mice treated with the AR agonist, there was an increase in matrix and fibroblast infiltration into the wounds (80). More recent studies have shown that a highly selective A2AAR agonist, sonedenoson, is a more potent promoter of wound healing compared to recombinant platelet-derived growth factor (becaplermin) (81). The role of A2AARs in promoting wound healing was further confirmed by observing that the selective A2AAR agonist promotes wound healing in wild-type mice but not in A2AAR knockout mice (81,82). In these studies, the healing wounds of wild-type mice treated with the A2AAR agonist exhibited a significant increase in the number of blood vessels compared to untreated controls. Although re-epithelialization was not delayed in the knockout mice, the absence of A2AARs was associated with disorganized granulation tissue. In contrast to these findings, Sun Fig-8: The role of adenosine A 2A and A 2B receptors in wound healing and inflammation and colleagues observed that N6-cyclopentyladenosine, a relatively selective A1AR agonist, promotes wound healing

(83).No confirmation was found in this study regarding the selectivity of the high concentrations of the agonist used for A1ARs or the potential involvement of A2AARs in mediating the observed phenomenon. These findings suggest that A2AARs play a role in promoting wound healing by regulating the functions of inflammatory cells, endothelial cells, and fibroblasts. Currently, sonedenoson, a topical A2AAR agonist, is being evaluated in Phase II clinical trials for its efficacy in treating diabetic foot ulcers (84).

Cordycepin



C. sinensis is a notable origin of cordycepin, a compound with various bioactivities (85). Cordycepin is a unique compound that has been recognized as a 3'-deoxyadenosine adenosine analogue. This means that it has a similar structure to adenosine, a nucleoside that plays a crucial role in many biological processes. However, cordycepin lacks the hydroxyl group at the 3' position, which gives it distinct properties and bioactivities. Research has shown that cordycepin exhibits a wide range of beneficial effects on human health. It has been found to possess anti-inflammatory, antioxidant, and immunomodulatory properties. These properties make cordycepin a promising candidate for the treatment of various diseases and conditions such as wound and cancer (86).

The limited research on cordycepin's specificity, selectivity, and sensitivity for adenosine receptor subtypes in skin cells, such as fibroblasts and keratinocytes, should be taken into consideration. Cordycepin likely acts as either an agonist or an antagonist for adenosine target pathways due to its structural similarity with adenosine. Notably, it has been reported to activate the adenosine A2A receptor, leading to spontaneous alteration behavior in the hippocampus (87). Additionally, cordycepin has been found to induce apoptosis in bladder cancer cells by activating the adenosine A3 receptor (88).

This study aimed to investigate the effects of adenosine and its natural derivative, cordycepin, on cultured human dermal fibroblasts. The researchers examined the expression pattern of adenosine receptor subtypes in fibroblasts and how they were activated by adenosine and cordycepin treatment. They found that the mRNA expression levels of CREB1 and Myc increased, and the intracellular cAMP concentration was elevated after treatment with adenosine and cordycepin. Additionally, mitochondrial energy metabolism was significantly improved. The activation of adenosine receptors by adenosine and cordycepin treatment stimulated the Wnt/β-catenin pathway in a reporter cell line, and the mRNA expression of Wnt target genes such as BMP2/4 and LEF1 increased in cultured fibroblasts. Adenosine and cordycepin treatment also led to increased phosphorylation of cell signal transduction elements, including mTOR and Gsk3b. Moreover, both adenosine and cordycepin enhanced the migration rate of fibroblast cells in cell scratch assays and stimulated the secretion of growth factors like IGF-1 and TGFβ3, which are important in wound healing. These findings suggest that adenosine and cordycepin activate the Wnt/β-catenin pathway through adenosine receptor activation, potentially promoting tissue remodeling in wound recovery. Additionally, GSK3b seems to play a crucial role in connecting the adenosine receptor and Wnt signaling pathways (89).

Examine the molecular mechanisms behind cordycepin's anti-inflammatory effects on activated macrophages. Cordycepin was observed to decrease the production of proinflammatory mediators and cytokines by deactivating

their corresponding genes at the transcriptional level. This was linked to the inhibition of MAPK and NF-κB signaling cascades. Additionally, cordycepin was found to interfere with LPS and TLR4 interactions in RAW 264.7 cells, leading to the inhibition of TLR4 signaling. Cordycepin can prevent the initiation of intracellular signaling cascades by regulating the binding of LPS to TLR4 on macrophages, as well as inhibiting MAPK and NF-κB activation (90).

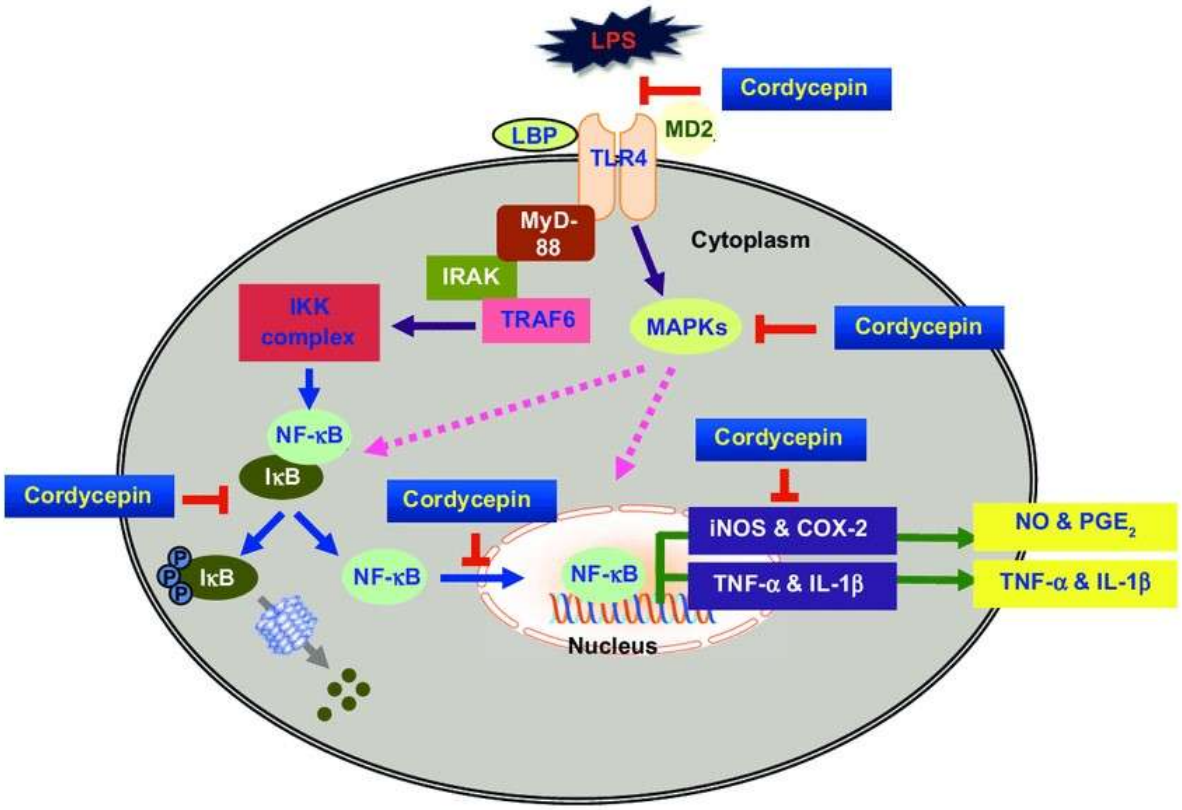


Fig 9:-Schematic figure of possible signaling mechanisms of cordycepin in inhibition of the LPS-induced inflammatory response.

Abbreviations:
LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; IL, interleukin; TNF-α, tumor necrosis factor-alpha; MyD88, myeloid differentiation factor 88; MAPKs, mitogen-activated protein kinases; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; IKK, inhibitor kappa B kinase; IRAK, IL-1R-associated kinase (90).

Effect of Wnt signaling pathway on wound healing
The Wnt/β-catenin pathway plays a pivotal role in the tissue regeneration process(91).The family of glycolipoproteins that regulates embryonic growth and homeostasis in adults is identified by the designation Wnt, which was named after the Wingless-linked integration site (92). The related signal is transmitted via the canonical or non-canonical Wntsignalling pathway, depending on the type of Wnt ligand. The central facilitator in the canonical Wnt pathway is β catenin, a co-activator of transcription (Wnt/β-catenin signalling). This signalling pathway is critical for cell proliferation, polarity, determination of fate and tissue restoration. Competitive antagonists bind to their specific receptors, blocking the Wnt/β-catenin signal transduction pathway. Wnt inhibitory factor-1 (WIF 1) and secreted frizzled-related proteins (SFRPs) (93) are common antagonists of Wnt/β-catenin signalling. Genetic defects, cancer and vascular diseases (94) are associated with defects in the Wnt/β-catenin pathway.

Humans have 19 Wnt members, including Wnt-1, Wnt-2, Wnt-2b, Wnt-3, Wnt 3a, Wnt-4, Wnt-5a, Wnt-5b, Wnt-6, Wnt-7a, Wnt 7b, Wnt-8a, Wnt-8b, Wnt-9a, Wnt-9b, Wnt-10a, Wnt-10b, Wnt-11, and Wnt-16 [95]. The Wnt/β-catenin pathway (Figure 2) is initiated by the binding of Wnt proteins to the seven-pass frizzled (Fz) transmembrane receptors and the co-receptor lipoprotein receptor-related proteins (LRP). In the absence of the Wnt ligand (OFF), a

protein complex consisting of axin, casein kinase (CK) 1, adenomatous polyposis coli (APC), and glycogen synthase kinase 3 beta (GSK3β) is formed. GSK3β phosphorylates β-catenin, leading to its degradation by proteasomes. When Wnt attaches to the Fz receptor (ON), the dishevelled (Dvl) protein is activated, deactivating the axin protein complex. This results in the accumulation of cytoplasmic β-catenin, facilitating its translocation to the nucleus and the formation of an active transcriptional complex with T cell-specific factor (TCF) and lymphoid enhancer-binding factor 1 (LEF1) for protein transcription [96,97]. Wnt3a primarily plays a role in activating the canonical Wnt/β-catenin pathway, and synthetic Wnt3a activates the Wnt/β-catenin pathway for cell proliferation and differentiation in vitro [98].

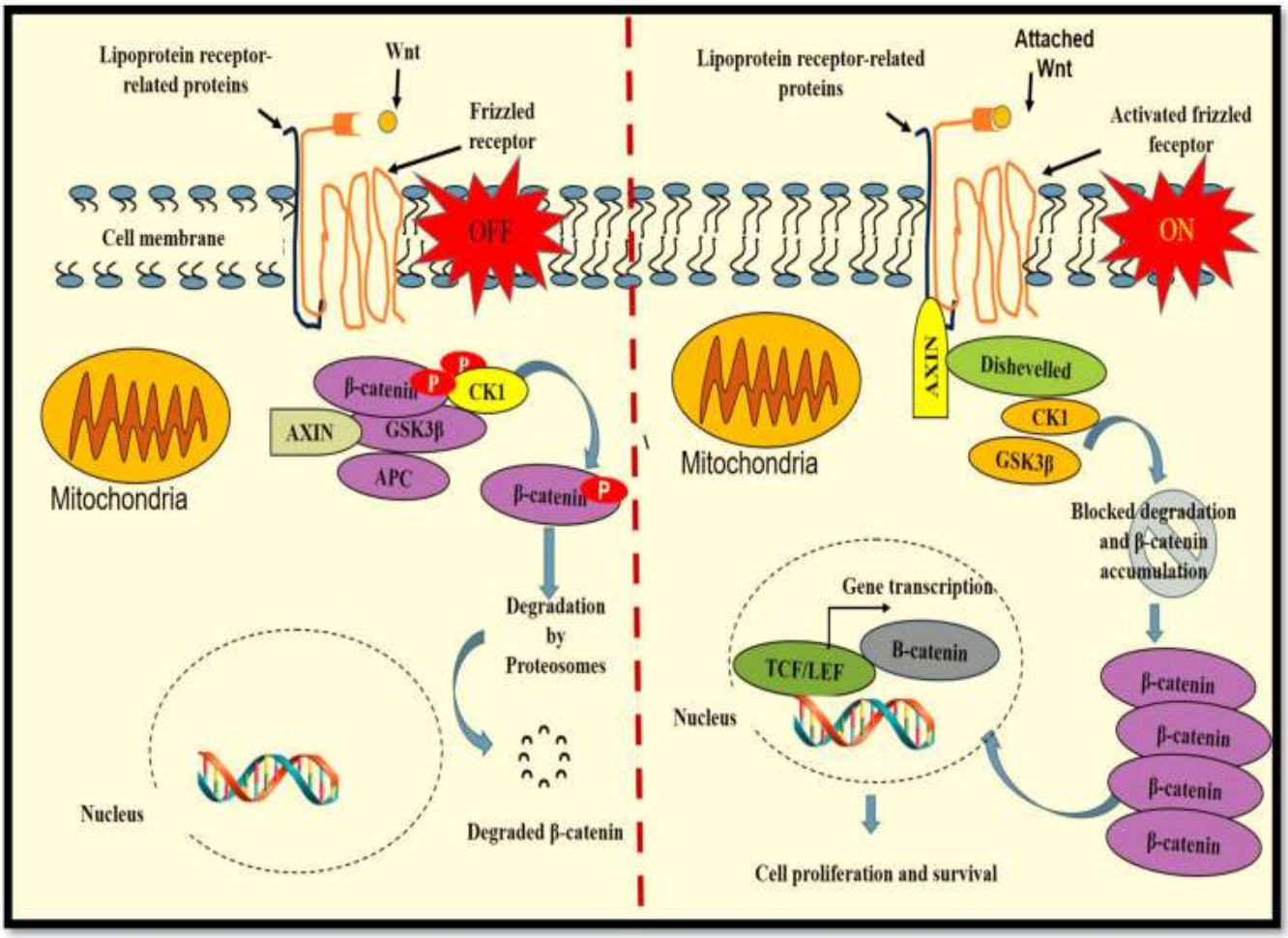


Fig 10:-The Wnt/β-catenin pathway.

The process of signal transduction is initiated when Wnt proteins bind to the seven-pass frizzled (Fz) transmembrane receptors and the lipoprotein receptor-related proteins (LRP). When the Wnt ligand is absent (OFF state), a protein complex consisting of axin, casein kinase (CK) 1, adenomatous polyposis coli (APC), and glycogen synthase kinase 3 beta (GSK3β) is formed. GSK3β phosphorylates β-catenin, which marks it for degradation. However, when Wnt binds to Fz (ON state), it activates the dishevelled (Dvl) protein, which inactivates the axin protein complex and leads to the accumulation of cytoplasmic β-catenin. This β-catenin is then translocated into the nucleus, where it forms an active transcriptional complex with T cell-specific factor (TCF)/lymphoid enhancer-binding factor 1 (LEF1) for protein transcription (99).

A significant amount of active communication processes take place in response to injury, ultimately leading to the restoration of wounds. The effectiveness of the wound restoration process is primarily determined by the differentiation and proliferation of various cells, such as fibroblasts, epidermal stem cells (ESCs), and keratinocytes, which are achieved through different biological signaling pathways. Abnormal regulation of cellular signaling can result in impaired wound healing, including the formation of chronic ulcers. The Wnt signaling pathway plays a

crucial role in controlling cell proliferation, movement, and differentiation during tissue restoration (96). In fibroblasts, the Wnt/β-catenin pathway is typically inactive but becomes frequently activated in response to injury (100). [Wang et al. (2017) (101)] identified a feedback control loop that connects basic fibroblast growth factor (bFGF) and Wnt signaling through β-catenin in fibroblasts. The bFGFWnt-regulated pathway is involved in cell proliferation, and inhibiting bFGF reduces the influence of Wnt signaling on cell proliferation. Basic FGF proteins are important mitogens in normal growth and wound healing (102,103).

The production of cytokines such as interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor (TNF)-α has been linked to Cordyceps species, their extracts, and bioactive components. Additionally, they promote phagocytosis in immune cells, boost nitric oxide production by increasing the activity of inducible nitric oxide synthase, and activate the inflammatory response via the mitogen-activated protein kinase pathway (104).

Intracellular signalling in wound healing

The initiation of the cell's response to injury is facilitated by growth factors and cytokines, which play a crucial role in the restoration of wounds. These biological agents achieve their effects through signal transduction. Throughout the various phases of wound healing, growth factors and cytokines have distinct functions (105). When injury occurs, they can activate multiple strategic signaling transduction pathways, which are primarily active during the development of embryonic skin (106). Tissue repair response is primarily mediated by extracellular signal-regulated kinases (ERKs) and calcium (Ca2+), which serve as the initial intracellular signaling molecules. These molecules regulate various biological activities, including cellular migration, proliferation, contractility, survival, and others that are associated with different transcription factors induced by various intracellular signaling pathways. Consequently, it becomes challenging to establish a direct link between a specific signaling response and injury (107). There is extensive interaction between intracellular signaling pathways during wound restoration, including those activated by epidermal growth factor (EGF) (108), transforming growth factor β1 (TGFβ1) (109), Src (110), Ras (111), integrin (112), Wnt/β-catenin (96), and Notch (113). The Wnt/β-catenin intracellular pathway regulates wound healing by enhancing wound neoangiogenesis, cell proliferation, differentiation, apoptosis, and tissue remodeling (114).

Conclusion:-

The Cordyceps mushroom is a beacon of potential and promise in the realm of regenerative medicine and wound healing. Its ability to stimulate cellular regeneration, modulate the immune system, and facilitate tissue repair is a testament to the power of nature and ancient healing traditions. Cordyceps offers a pathway to the future of healthcare, paving the way for innovative treatments and therapies that can transform the lives of those in need. Ongoing research and growing evidence surrounding Cordyceps demand our attention and investment. With its regenerative potential, Cordyceps may redefine the boundaries of modern medicine and serve as a source of hope for those seeking effective solutions for regenerative therapy and wound healing. It is our responsibility to nurture and explore this potential, ensuring that the promise it holds becomes a reality for those seeking a healthier, happier future.

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