REVIEW ON SYNERGISTIC DRUG DELIVERY OF PHARMACEUTICAL DRUGS USING NATURAL SNAIL MUCIN

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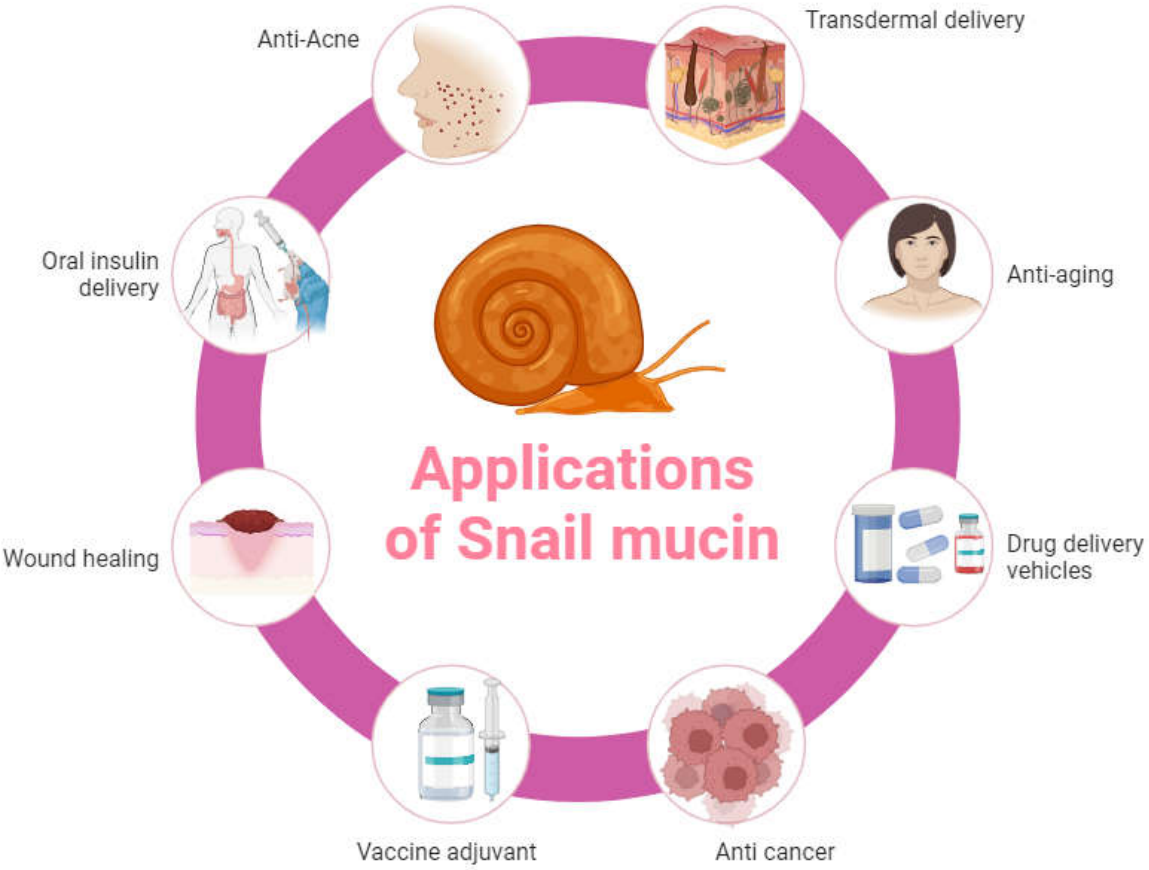
ABSTRACT:

The global market for snail mucin in dermatological applications is projected to experience substantial growth by 2024. Recently, it has developed significant attention for its therapeutic potential in the pharmaceutical field. In skincare, snail mucin is celebrated for its regenerative properties, attributed to a complex blend of glycoproteins, hyaluronic acid, glycolic acid, and various growth factors. These components promote skin hydration, repair damaged tissues, and enhance elasticity, making it a popular ingredient in anti-aging and wound healing products. In contrast, snail mucin's applications in the pharmaceutical field extend beyond skincare. Recent research highlights its potential in wound healing, where its antimicrobial and anti-inflammatory properties aid in reducing infection risk and accelerating tissue regeneration. Also, snail mucin is used as delivery vehicle for the administration of oral and rectal insulin. Beyond this, snail mucin exhibits potential therapeutic benefits in transdermal delivery and cancer. In conclusion, this review has summarised the various applications of snail mucin in the pharmaceutical field, encompassing its roles in wound healing, oral insulin delivery, and potential advancements in drug delivery systems.

KEYWORDS: Biomedical applications of mollusks, Natural polymer drug delivery, Snail mucin-based drug delivery system, Wound healing.

GRAPHICAL ABSTRACT:



INTRODUCTION:

The mucous secreted by snails contains mucin proteins, which serve a variety of biological purposes such as adhesion, lubrication, and microbial protection. Mucins are a broad class of highly glycosylated proteins. Snail mucins have recently emerged as an enormous repository of novel concepts with a broad range of uses in biology, chemistry, medicine and biological technology. Mainly snail mucin is used tremendously in skin care industry and also its emerging in drug delivery (1). Snail mucin and its extract has gained popularity in several areas of dermatologic care and also in drug delivery system as a therapeutic agent and as a carrier. Pharmaceutical excipients derived from animals has been growing recently because most animal products and by-products are safer, more environmentally friendly, and biocompatible than synthetic materials. As a result, they serve as good replacements for synthetic products (2). Although the animal origins and techniques of collecting of snail mucin are fascinating, research is still ongoing to fully understand the possible applications of its ingredients. This review aims to discuss the various applications of snail mucin in drug delivery.

Historical Background of Snail Mucin

The Greeks were the first people who used the mucus slime trails left by snails and slugs because they believed that mucin had anti-inflammatory and anti-aging qualities (3). Hippocrates, who proposed the use of snail mucus to treat protocoele, and Pliny, who thought that snails speed up the delivery process and described them as "a sovereign remedy to treat pain related to burns, abscesses and other wounds" lived about 460 BC. Along with many other health conditions, Pliny also suggested using snails to treat stomach problems and nosebleeds. Celse thought crushed snails, or snails without their shells, were thought to have medicinal healing properties. It is said to possess emollient characteristics when boiled. In those period People who had dizziness, fainting episodes, or outbursts of insanity were advised to consume snails (4). Historic records also note Chilean snail farmers found snail mucin to help heal skin lesions without scarring, and the Han Dynasty in China documented its use in children's tetanus, insect bites, and hemorrhoids (5,6). In 19th century witnessed a rise in interest in the use of snails for pharmaceutical and medical purposes.

Further proof of this may be found in a book written in 1808 by George Tarenne titled "Snails and their ability to cure hernias." In 1817, as per the New Natural History Dictionary, snails may be collected for medicinal purposes and are suggested as a throat broth and for females, a smoother combination is beneficial and can be used to maintain a smooth and radiant skin surface. First and second-degree tuberculosis, intestinal irritations, acute and chronic chest infections, and resistant colds were all treated with oral snail formulations. Only external use of snail ointment is appropriate for treating unpleasant chapping and efflorescence. In addition to Helix pomatia, Figuier lists the properties of hélicine, a transparent yellow oil extracted from "all big species of snails". The French medicinal reference book Dorvault, published in 1877, also listed several medications made from snails. Baron-Barthelemy, a chemist from Beziers, Haut-Rérault, France, published a study about the helicine-based pharmaceutical formulations permitted for the 1855 Universal Exhibit (4). The 1945 version of Dorvault still has an entire paragraph regarding snails, indicating that snails are being used medicinally. In 1953, Quevauviller conducted a thorough analysis of the medicinal potential of snails in France (4). Helix pomatia agglutinin (HPA) is a lectin identified from common snails which is used as

prognostic indicator for breast, stomach and colon cancer. Glycoproteins related with HPA are connected to cancer metastasis. Snail mucin are rich in fatty acid (α -linolenic acid) which prevents heart related conditions (1). In 2004, FDA approved ziconotide (SNXIII) a non-opioid analgesic Prialt (intrathecal infusion) for the treatment of severe chronic pain. More than 1,200 individuals participated in three Phase III clinical studies and received ziconotide testing prior to FDA clearance. ziconotide obtained from the toxin of the cone snail species Conus magus (7). Snail mucin has increased its value in skin care products, and the skin care industry is expected to reach $770 million by 2025 (8). Though it has various uses, snail mucin is still underdeveloped and is expected to grow in various biological and cosmeceutical fields.

SNAIL

He used snail mucus to create a natural bio-adhesive utilising polyanionic glycosaminoglycan and the network of positively charged proteins. He also insisted that multiple interactions allow the deformable bulk adhesive matrix to stick to moist tissue. In both normal and diabetic male rats, mucin exhibited good haemostatic action, biocompatibility, and biodegradability. It also responded well to speed up the healing of full-thickness skin lesions. Additional mechanistic research demonstrated that it considerably enhanced angiogenesis and epithelial regeneration, reduced inflammation in chronic wounds, and efficiently encouraged macrophage polarisation towards the anti-inflammatory phenotype. The primary active constituent is a substantial glycosaminoglycan component that resembles heparin (9).

Lawrence B. Etim et.al., concluded that mucus secreted by snails could be a best source for natural antibiotic that can be replaced with expensive artificial antibiotic agents used in wound healing. Additionally, he looked at the in vitro antibacterial activity of mucus secretions from Achatina fulica, Achatina marginata ovum, and Archachatina saturalis. The mucus minimum inhibitory and minimum bactericidal concentrations were also assessed. The results shown that Staphylococcus sp. were more susceptible than those two species to mucus secretion from A. fulica (15.4±2.04) and A. marginata saturalis (17.4±1.20) (10).

Adikwu M.U et.al., has assessed the impact of snail mucin on wound healing in combination with Brachystegia eurychoma gel and honey. A wound induced via excision model in rats was treated with a combination of snail mucin, honey, and Brachystegia eurycoma gum at varying doses. It has been demonstrated that applying mucin to the Brachystegia eurycoma gel in combination with honey speeds up the healing process compared to using mucin in isolation. Additionally, the use of Brachystegia eurycoma gum alone was found to enhance the healing of wounds. Within fifteen days following therapy, full recovery was seen. In order to heal wounds, pharmaceutical formulations containing honey, mucin, and Brachystegia eurycoma gel should be utilised. When used in the proper amounts with mucin and honey, Brachystegia eurycoma gum encourages the regeneration of hair follicles, inhibits the spread of germs, and heals wounds (11).

Danielle G. Lacanilao et.al., evaluated the wound healing property of Pomacea canaliculata mucin by extracting the mucus. They assessed the effective of wound healing by treating with three groups of Sprague-Dawley rats. Groups 1 and 2 represented the groups that received Snail Mucin treatment, Solcoseryl Jelly positive control, and untreated negative control, respectively. Based on the histological condition and percentage of wound contraction, the wound healing

property were evaluated. In terms of % wound contraction and wound area reduction, the group treated with snail mucin showed the second-fastest rate of improvement. In terms of % wound contraction and wound area reduction, the group treated with snail mucin showed the second-fastest rate of improvement (12).

Table 1: Different types of Mollusca species whose mucin has found use in a variety of biological and biotechnological *fields* (1).

S. No	Biological Name	Common Name	Uses	Images
1.	Archachatina marginata	African giant snail, banana rasp snail	To treat liver diseases, anaemia, Wound healing, Antibiotic drug delivery	
2.	Cornu aspersum (syn. Helix aspersa, Cryptomphalus aspersus)	Brown Garden snail	possesses benefits of healing for human skin, including glycolic acid and allantoin	
3.	Achatina (Lissachatina) fulica	Giant African land snail	Osteoarthritis, Wound healing	
4.	Helix pomatia	Roman snail, Burgundy snail, or escargot	Helix pomatia agglutinin (HPA)-Lectin	
5.	Arion fuscus	Dusky arion	Medical adhesives	
6.	Tikoconus costarricanus	Micromollusks	Antimicrobials to inhibit pathogens, lubrication	

7.	Pomacea canaliculata	Golden Apple snails	Wound healing	

PHARMACEUTICAL APPLICATIONS OF SNAIL MUCIN:

Snail Mucins in Transdermal Delivery

M.I. Arhewoh et.al., assessed the mucin-based transdermal patches containing bovine serum albumin (BSA) for their ability to enhance penetration and their bio adhesion characteristics. Precipitated mucin was used to make several batches of transdermal film patches containing bovine serum albumin. Differential scanning calorimetry analyses showed no interactions between BSA and mucin. For every patch, the bioadhesion values varied between 1.70 and 1.98 g/sec. After a 12-hour period, 47% of the medication had permeated the skin of the treated rats using acetone-precipitated mucin patches. Snail mucin therefore possessed both the bio adhesive feature and the penetration-enhancing effect due to its potential as a transdermal delivery in the development of Bovine serum albumin patches (13). Matthew I Arhewoh et.al., had demonstrated transdermal delivery by patches using Ibuprofen. Multiple batches of IBF loaded transdermal film patches were made using the precipitated mucin and varying volumes of polyethylene glycol (PEG) as plasticizer. The drug concentration, in-vitro and ex-vivo (skin penetration) release profiles, weight homogeneity, patch thickness, folding durability, moisture content and absorption, and bio-adhesion of the produced patches were evaluated. Snail mucus has a bio-adhesion property and a medication release profile that make it an appropriate transdermal drug delivery patch (14). Di Filippo, Maria Francesca et.al., formulated and evaluated novel biodegradable and natural bio adhesive patches using Gelatin and snail mucin loaded with Fluconazole drug incorporated in it. The amount of snail slime in a formulation greatly influences its characteristics. Specifically, formulations with greater snail mucin concentrations are more flexible and elastic, and the snail slime gives the films their desired skin-adhesive qualities. Snail slime impedes fluconazole recrystallization inside the film and facilitates drug solubilization into the film-forming fluid. Furthermore, it has been demonstrated that snail mucus is essential for preserving the amorphous state during storage for up to six months (15).

Snail Mucins in Insulin Oral Delivery

Mumuni, Momoh A et.al., prepared insulin-loaded nanoparticles (NPs) using the self-gelation process in order to evaluate the oral administration of insulin. As natural polymers, chitosan and water-soluble snail mucin were employed. The in vitro release of insulin in acidic and phosphate buffer was evaluated, and the hypoglycaemic action was evaluated in rats with diabetes. Insulin was delivered for eight hours in a continuous release fashion. In vivo investigations demonstrated a considerable hypoglycaemic effect in diabetic rats after peroral administration of the insulin-loaded NPs, as compared to the effect of free oral insulin solution. The results of the toxicological and pharmacokinetic studies also showed that the NPs formulations were well-biocompatible, showing no hepatotoxicity and little insulin plasma

clearance in addition to no cell viability. Insulin may now be preserved and administered orally more effectively thanks to the production of insulin nanoparticles made of chitosan and snail mucin (16).

Franklin Kene Chukwu et.al., He produced insulin-loaded microparticles to assess insulin delivery orally. The Insulin loaded MPs were encapsulated with chitosan and snail mucin and the release were observed. The size of the generated insulin-containing microparticle was less than 440 μm, which is suitable for oral absorption. Over the course of ten hours in vitro, the drug was constantly delivered, with a sizable portion of the medication (>80%) encapsulated. The positive zeta potential indicated that the medication had been incorporated in the core of the polymer. Because insulin's hypoglycemic qualities were maintained, blood glucose levels dropped significantly (by more than 50%) and had long-lasting effects that persisted for more than ten hours in vivo. According to this study, produced insulin-MPs might be useful as carriers for insulin administered orally (17).

Mumuni A Momoh et.al., Using ratio mixes of Tween 80 and snail mucin, he developed an insulin-loaded microemulsion intended for oral administration. In order to give extended release, improved in vivo stability, and improved medication absorption in the gastrointestinal tract, they employed snail mucin to load insulin into the inner core of the produced water-in-oil microemulsion. The results showed that blood glucose levels were successfully decreased by insulin-loaded microencapsulation for a duration of more than 8 hours after oral delivery. Over ten hours of in vitro release were sustained, and an encapsulation efficiency of more than 70% was attained. As a result, they suggested that the developed oral insulin formulation may serve as a workable alternative dosage form for the oral delivery of proteins (18).

Snail Mucins in Insulin Rectal Delivery

M.U. Adikwu et.al., attempted many formulations for the rectal absorption of Insulin-Mucin complex. This study investigated the stability of insulin with mucin and the feasibility of rectally administering insulin with snail mucin acting as the delivery vehicle. According to the study, the amount of insulin adsorbed on the mucin powder decreases as temperature rises. The effect of insulin stabilised in mucin at different concentrations and exposed to varied temperature conditions on the experimental animals' % basal blood glucose level showed that the stability of the insulin decreased with increasing temperature, as demonstrated by the animals' decreased plasma glucose levels. When compared to the non-significant blood glucose reducing impact of non-stabilized insulin given to the control group of rats, the insulin stabilised in mucin demonstrated an improved lowering of the plasma glucose level to 49%. As a result, a safe technique for rectal insulin administration might be developed using snail mucin combined with insulin (19).

Snail Mucin in Cancer Treatment

El Ouar et.al., investigated that Helix aspersa extract affected the malignant inhibitor genomes, TNFα, and NFκB in the breast cancer cell line Hs578T. Extract from Helix aspersa, rich in bioactive compounds, had shown promise in cancer therapy by inducing apoptosis and inhibiting proliferation. It modulates TNFα levels and attenuates NF-κB signaling, suggesting

anti-inflammatory and anti-proliferative effects. Furthermore, the extract potentially influences tumor suppressor genes crucial for cell cycle regulation and genomic stability. These results highlight its potential as a natural therapeutic agent for the treatment of breast cancer and need further more investigation into its molecular mechanisms and clinical benefits (20).

Ellijimi et.al., proved that snail mucin has anti-tumoral efficacy against human melanoma cells in addition to its ability to cure melanogenesis. In fact, SS decreased tyrosinase activity and melanin concentration in B16F10 cells. It is noteworthy that B16F10 cells and nontumorigenic HaCaT cells were not affected by SS. The results support the use of Snail slime for skin problems and provide insight into its possible anti-melanoma impact (21).

Snail Mucins in Pneumonia Treatment

Thaddeus Gugu et.al., examined the synergistic relationship between lincomycin and natural snail mucin in immuno-chemotherapy against Streptococcus pneumoniae infections using checkerboard assessments. The antibacterial and immunomodulatory properties of snail mucin increase the effectiveness of antibiotics. Snail mucin and Lincomycin, which is efficient against gram-positive bacteria such as S. pneumoniae, are mixed to investigate possible synergies. Previous studies have demonstrated how snail mucin may break down biofilms and increase bacterial sensitivity in order to enhance immune responses and potentiate medications. Using checkerboard assays, the study evaluated the quantitative relationship between snail mucin and lincomycin, with an emphasis on strengthening immune defences against S. pneumoniae and preventing bacterial growth (22).

Snail Mucin as Adjuvant in Hepatitis B Vaccine

Joshua PE et.al., He assessed the effectiveness of snail mucin as a recombinant Hepatitis B vaccine adjuvant. Studies on the interaction between HBsAg and a homology-modeled snail mucus protein revealed a stronger contact between the HBV antigen and the antibody. which was based on in silico prediction. Experimental mice showed no negative reactions to the snail mucin-adjuvanted rHBsAg vaccination. According to this study, recombinant hepatitis B surface antigen immunisation could benefit from the safe and effective use of snail mucin as an adjuvant. It produces the appropriate immune responses and was highly accepted. Immune responses were continuously activated as a result of the vaccine antigen's continued release over timeThe proposed approach directly lowers the number of doses or injections required to achieve protective antibody levels based on the prime and booster doses of recall immunizations (23).

Snail Mucin Used in Gastric Ulcer

Amah Akuma Kalu et.al., investigated the effects of the mucin generated by Archachatina marginata on gastric ulcer-challenged rat stomach tissue. The amount of pepsin activity, free and total acidity, and gastric juice volume were all significantly reduced, along with the amount of acid produced by the stomach. According to this study, A. marginata mucin may be an acceptable option for the development of drug to cure gastric ulcers (24).

Table 2: Various species of snails used in drug delivery and their findings.

S. No	Drug	Species of Snails	Reference
1.	Dried Snail-Mucus (D-SMG)	Achatina fulica and Helix lucorum	(9)
2.	Snail Mucin	Three species: Achatina fulica, Achatina marginata ovum, and Achatina marginata saturalis	(10)
3.	Brachystegia Eurycoma Gum + Snail Mucin	Archachatina marginata	(11)
4.	Snail Mucin	Pomacea canaliculata	(12)
5.	Bovine Serum Albumin + Snail Mucin	Archachatina maginata	(13)
6.	Ibuprofen	Archachatina maginata	(14)
7.	Fluconazole + Snail Mucin + Gelatin	Helix Aspersa	(15)
8.	Insulin-Loaded Nanoparticles + Chitosan + Mucin	_	(16)
9.	Microparticles Infused With Insulin + Chitosan+ Snail Mucin	Achatina fulica	(17)
10.	Insulin+ O/W Emulsion + Snail Mucin	Achatina fulica	(18)
11.	Insulin-Mucin Complex	Archachatina maginata	(19)
12.	Triple Negative Breast Cancer Cell Line Hs578T + Snail Extract	Helix aspersa	(20)
13.	Helix Aspersa's Mucin	Helix aspersa	(21)
14.	Snail Mucin + Lincomycin	Achatina fulica	(22)
15.	Snail Mucin + Hepatitis B Vaccine	Archachatina marginata	(23)
16.	Archachatina Marginata's Mucin	Archachatina marginata	(24)

Figure 1: Advancement of Snail Mucin

CONCLUSION:

In conclusion, while snail mucin has gained significant recognition and utilization in the skincare industry for its anti-acne, hydrating, and anti-aging properties, its potential in the pharmaceutical field remains largely untapped. Beyond skincare, snail mucin holds immense promise as a valuable resource in pharmaceutical applications. Its proven benefits in wound healing, oral insulin delivery, anti-cancer agents, and drug delivery vehicles highlight its versatility and therapeutic potential. Moreover, the use of snail mucin in oral and rectal insulin delivery systems underscores its role as a bioactive substance capable of enhancing drug bioavailability and efficacy. As research continues to unveil its diverse pharmacological properties, snail mucin contributes significantly to advancements in medical treatments and therapies, and expanding the scope of pharmaceutical innovation. Thus, exploring and harnessing the full spectrum of snail mucin's benefits in pharmaceutical applications is a promising avenue for future research and development.

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