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السليمارين في صناعة الأدوية: تحديات الاستخلاص والتركيب والتوافر البيولوجي والتسويق

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المستخلص :

إن الأبحاث حول السليمارين تزدهر نحو مستقبل واعد. ومن المتوقع أن يلعب السليمارين دورًا رئيسا في تطبيقات حماية الكبد ومكافحة السرطان والأمراض العصبية التنكسية، حيث من المتوقع أن تؤدي التحسينات الواعدة المستمرة في أنظمة التغليف الحيوي الدقيق وأنظمة التوصيل (تركيبات الجسيمات النانوية، والتغليف الليبوزومي، وما إلى ذلك) إلى زيادة التوافر البيولوجي بشكل كبير ومن ثم فعالية السليمارين كمركب علاجي. يتم استعمال خصائصه المضادة للأكسدة والالتهابات القوية ويتم البحث عنها لمجموعة من الأغراض بما في ذلك الجلد، وشفاء الجروح، وصحة الأمعاء. فضلاعن ذلك، هناك اهتمام يحيط بالتأثيرات التآزرية المحتملة للسيليمارين بالاشتراك مع طرق علاجية أخرى، بما في ذلك العلاج الكيميائي أو العلاج المناعي. ستمكن الدراسات حول دوره في الطب الشخصي من جعل العلاجات أكثر ملاءمة للملف الجيني للفرد، مما يجعل السليمارين خيارًا أكثر فعالية لحالات مثل متلازمة التمثيل الغذائي أو أمراض الكبد. إن الابتكارات في الأساليب الصديقة للبيئة لزراعة واستخراج السليمارين سوف تساهم في زيادة الطلب بطريقة تحمي كوكبنا مع تحول العالم نحو الاستدامة. وإذا استمر السليمارين في الوفاء بوعده بتطبيقات محتملة واسعة النطاق، فقد يصبح في يوم من الأيام سلاحًا علاجيًا حاسمًا في الطب الحديث.

الكلمات المفتاحية : سيليمارين، التركيبة الصيدلانية، التوافر البيولوجي، تقنيات الاستخلاص، تحديات السوق.

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Silymarin in the Pharmaceutical Industry: Extraction, Formulation, Bioavailability, and Marketing Challenges

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Abstract:

Research around silymarin is blossoming towards a hopeful future. Silymarin is expected to play a key role in hepatoprotection, anti-cancer, and anti-neurodegenerative disease applications, as ongoing promising improvements in bio-microencapsulation and delivery systems (nanoparticle formulations, liposomal encapsulation, etc.) are expected to dramatically increase bioavailability and thus the efficacy of silymarin as a therapeutic compound. Its potent antioxidant and anti-inflammatory properties are used and researched for a range of purposes including, skin, wound healing, and gut health. Additionally, there is interest surrounding the potential synergistic effects of silymarin in combination with other treatment modalities, including chemotherapy or immunotherapy. Studies of its role in personalized medicine will enable treatments to be more tailored to an individual's genetic profile, making silymarin an even more effective choice for conditions like metabolic syndrome or liver disease. Innovations in eco-friendly methods of growing and extracting silymarin will contribute to the increased demand in a way that protects our planet as the world shifts toward sustainability. If silymarin continues to deliver on its promise of broad-ranging potential applications, it may one day become a critical therapeutic weapon in modern medicine.

Key words: Silymarin, Pharmaceutical Formulation, Bioavailability, Extraction Techniques, Market Challenges.

Introduction to Silymarin and its Pharmaceutical Potential:

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Silymarin represents a complex mixture of bioflavonoids found in the fruits and seeds of milk thistle, garnering extensive attention for its exceptional capabilities. This phytocompound has been largely publicized since antiquity. Presently, plants such as milk thistle and the extracts derived from them are of prime interest to numerous researchers as well as pharmaceutical industries (Abenavoli et al., 2018)(Bijak, 2017).

Silymarin possesses a vast array of pharmacological activities, including hepatoprotective, immunomodulatory, antioxidant, anti-inflammatory, and anticancer effects, among several others (Hellerbrand et al., 2017). Present-day pharmaceutical industries seek to uncover plant-derived constituents to drive their intense focus on the exploitation of plant-based therapeutics versus the exploitation of synthetic drugs (Nasim et al., 2022). Plentiful evidence demonstrates the favorable risk-benefit ratio of silymarin with its exceptional therapeutic potential in the benign therapy of certain types of liver diseases, as well as a variety of other extrahepatic diseases. Silymarin has been an attractive topic in the mainstream. It is an adjunct therapeutic strategy in various kinds of liver diseases(Jaffar et al., 2024).

In a 4-month randomized double-blind clinical study, 51 type II diabetics in two well-matched groups participated. The first group (n = 25) received silymarin (200 mg) tablets three times a day and conventional therapy. In the second group (n = 26), silymarin was replaced with a placebo tablet. Patients were visited monthly, and HbA1c, FBS, insulin, total cholesterol, LDL and HDL, triglyceride, SGOT, and SGPT levels were measured before and after the trial. Silymarin-treated individuals had significantly lower HbA1c, FBS, total cholesterol, LDL, triglyceride SGOT, and SGPT levels than placebo at the start of the research (Huseini et al., 2006) .

One hundred people with non-alcoholic fatty liver disease were sent for liver disease treatment based on results from an ultrasound, higher levels of alanine and aspartate aminotransferases (ALT and AST), or a liver biopsy. A placebo was given to patients in Group A, whereas 280 mg of silymarin was given to those in Group B. Each patient underwent a 24-week course of

treatment with checkups scheduled at the outpatient clinics every four weeks. Patients with NAFLD who take silymarin seem to see considerable improvements in biochemistry and a reduction in transaminase levels (Hashemi et al., 2009).

Sixty-four patients diagnosed with NASH were assigned to one of two groups: a case group consisting of 33 patients and a control group consisting of 31 patients. An abdominal sonography and a steady rise in aspartate and alanine aminotransferase levels over 1.2 times the upper normal limit in the last six months were needed to be included. The case group was given 210 mg of silymarin orally daily for 8 weeks, while the control group got a placebo. The patients underwent a second evaluation at 8 weeks to determine their AST and ALT levels. Hepatic enzyme levels dropped much more in the silymarin group of individuals (Solhi et al., 2014).

Two groups of 85 patients were assigned: those with nonalcoholic fatty liver disease (group A) and those with HCV-related chronic hepatitis and nonresponders to treatment (group B). The treatment was silybin/vitamin E/phospholipids. Group A's liver steatosis ultrasonographic scores dropped significantly after treatment. Treating patients improved liver enzyme levels, hyperinsulinemia, and liver fibrosis indicators. The study looked at steatosis degrees, insulinemia, plasma levels of TGF-β and TNF-α, fibrosis indexes, and γ-glutamyl transpeptidase. Silybin conjugated with vitamin E and phospholipids may be a supplementary treatment for chronic liver disease, according to findings (Loguercio et al., 2007).

The proprietary botanical drug came on the pharmaceutical market 84 years ago (Upton et al., 2024). Numerous clinical trials conducted worldwide have confirmed the efficacy and safety of silymarin. Nonetheless, the global commercialization of silymarin has been retarded due to some toxicological issues pertaining to both the impurity and the degradation byproducts of Silymarin and the long-term use of synthetic pharmaceuticals containing silymarin (Camini & Costa, 2020). Currently, silymarin-derived drugs are being utilized as adjunct therapy in diseased individuals in lieu of long-term therapy purposes (Ralli et al., 2021).

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Extraction Techniques for Silymarin:

The extraction of silymarin from milk thistle encounters several challenges. Low yield and efficiency of silymarin extraction from milk thistle presents one of its greatest challenges in terms of obtaining high yield through effective techniques. Traditional techniques such as Soxhlet extraction are frequently stated to necessitate long processing periods and bulk solvents (Fenclova et al., 2020). The requirement for organic solvents in traditional extraction methods results in environmental and safety challenges, in addition to raising product costs (Wianowska & Wi niewski, 2015). The silymarin is sensitive to heat; thus, extraction processes at a high temperature could reduce the active compounds, thus reducing the effectiveness of the extract (Fenclova et al., 2020). Most traditional extraction techniques lack selectivity, which leads to extracting unwanted compounds along with silymarin and impacts the purity and quality of the final product (Ong, 2004).

The quality and yield of silymarin depend on the methods of extraction, which are the direct spots of investigation for a commercially valuable product. Established protocols are able to automatically assure a high yield and maintain the properties and chemical composition up to standard (Lorenzo et al., 2020). The two main methods for the laboratory and industry for the extraction of silymarin are the schemes falling under conventional and modern techniques (Saleh et al., 2017).

The conventional method dates back thousands of years and is still in practice even in the present scenario (Wianowska & Gil, 2017). The commonly used techniques under this head include maceration and percolation methods, where the raw material is soaked in solvent for several days so that the solvent favors the separation of active ingredients from the gunk (Jabłonowska et al., 2021). One of the bottlenecks of conventionally used techniques is the use of excessive quantities with an overlook of the chemical and physical properties of the ingredients. Additionally, it takes a long time to extract this necessity. Last but not least, too much heat destroys or changes the secondary metabolites of the components, which means that

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the end product can't have any therapeutic effect (Jahan et al., 2016)(Đorđević et al., 2018).

Although the traditional method is barbaric, a progressing modality is taking place under the modernization of methods (Đorđević et al., 2018). Obtaining a silymarin-rich fraction is important not only for a guarantee of the constant quality and safety of the final product but also for manufacturing millions of tons for pharmaceutical purposes. Thus, through natural sources of flavones, silymarin should be added to the list of medicinally marketed agents, not as a health ingredient, because healthcare requires a fraction of single-component nature (Aziz et al., 2021). This is why various extractive techniques have been reported for silymarin, traditionally and innovatively, supplementing the medically pharmaceutical product (T. Zhang et al., 2024). Widespread methods, which have been used for extracts leading to the million-league precincts yearning for recent entry, are summarized in the next few sections.

- **Traditional Extraction Methods**

Various chemical components such as flavonolignans and flavonols can be isolated from the milk thistle plant. Among them, silymarin compounds obtained from the fruit of the plant are widely used for their beneficial properties, especially liver protection (Csupor et al., 2016). The compounds have been extracted with several conventional procedures. The first step of the extractions was generally the cutting and slicing of the plants into small parts to increase the solvent–solute contact surface. Three of the most-used maceration procedures are simple extraction, percolation, and infusion (Sprung et al., 2023).

The time of the maceration procedures is related to the diffusion of the main solute compounds in the solvent, which is required to lay a film of the solvent on the solid drug surface for the continuous deposition of the compounds, starting from the boundary layer with the solvent and moving towards the surface (Gilabadi et al., 2023). It is known that the procedures are generally performed in a laboratory, where wide neck and flat bottom flasks are common. Therefore, another procedure equivalent to percolation

and infusion is the stirring extraction, which is basically a maceration extraction operating under intensive stirring (Cárdenas & Lucena, 2017) .

The main steps of the mentioned conventional extractions performed in the laboratory could be represented as follows: cutting plants, preparation of solvent, addition processes, and ideal time for extraction. Each single extraction process for each single plant drug resulted in different yield fractions of the main compounds, depending on the drug parts used and the solvents used. These methods provided high potential extraction for each drug and compound, such as silymarin compounds, using nonconventional solvent systems (Giacometti et al., 2018).

- **Modern Extraction Technologies:**

Downstream processes, such as product extraction and isolation, are usually expensive in terms of both time and money (K. A. Bunnell et al., 2010). Often, using common extraction techniques can have several disadvantages, such as using too much solvent in the process or having to use extreme extraction conditions. Consequently, several innovative extraction methods have been developed to address these disadvantages, some of which are still being completed (Mohammed Golam Rasul, 2018).

Supercritical fluids extraction: Many researchers working on the molecule include supercritical fluids in their work because of their particular technological aspects (Palaric et al., 2023). Several derivatives, such as supercritical carbon dioxide or supercritical sulfur hexafluoride, can be used to perform extractions of varying efficiency. Indeed, working in the supercritical fluid region allows solubility and diffusion to be enhanced at the same time, making separation more efficient (Çelik & Gürü, 2015). In addition, you can change the solvent characteristics by operating selectively below, at, or above the critical point. It also has the advantage of operating with chemically inert, non-toxic, or eco-friendly solvents (Naziri et al., 2016).

Supercritical fluid extraction methods are becoming increasingly popular. Supercritical anti-solvent extraction and supercritical fluid extraction with polar solvents are two of the most popular procedures (T. Ahmad et al., 2019). These methods are quick and specific, and they can

yield high concentrations while minimizing the use of solvent. Solvent and energy consumption, reaction time, extrinsic metal and impurity waste production, and automation potential are all evaluated (Herrero et al., 2010).

Although supercritical fluid extraction is more time-consuming and cumbersome than more conventional methods, it is considered the most suitable in the pharmaceutical field for the extraction of bioactives, fatty components, and essential oils, as it often offers the advantage of better conservation of active product molecules (Bhusnure et al., 2016). These new optimized sequential and simultaneous extractors are offered most often by financial corporations. However, the equipment and system costs for these new profitable and eco-friendly systems need to be carefully evaluated before trading. Commercial and industrial evaluations should be used to examine the relative cost benefits of this method, as well as the cost of equipment if freshly produced food supplements are to be formulated (Prado et al., 2017).

Microwave-assisted extraction: It is mainly used for selective and efficient extraction. Additionally, it has the advantage of reducing extraction time and the solvent required (Fathi-Achachlouei et al., 2019). Ultrasound-assisted extraction: Similar to microwave-assisted extraction, the objective of ultrasound extraction is to improve extraction yields and reduce extraction times while working predominantly in alcoholic media. This has now become an advantageous extraction technique and is used in many laboratories to isolate fatty substances or other bioactive molecules (Drouet et al., 2019). The use of ultrasonic waves to increase the penetrability of the solvent, which in turn speeds up the extraction process. It is faster, can be performed at lower temperatures, and can be used to enhance extraction efficiency, lowering energy needs and use of damaging solvents (Arya et al., 2021)

Recent strategies have arisen that can be incorporated with contemporary extraction methods, potentially enhancing their efficacy. Enzyme-assisted extraction: The application of appropriate enzymes that decompose cell walls and increase the release of silymarin is a more specific extraction method and could enhance the extract yield. So it could be more

sustainable and more eco-friendly (Puri et al., 2012). Integration of Artificial Intelligence (AI): It could assist in designing and optimizing extraction methods, monitoring the process in real-time, and ensuring that the parameters are always ideal for maximizing yield and purity (Vinchurkar & Mane, 2024).

Formulation Strategies for Silymarin:

The formulation is an essential part of silymarin's pharmaceutical product for successful administration. This is important because the rapid increase in silymarin bioavailability promotes the application in various diseases and injuries (Di Costanzo & Angelico, 2019). This section will therefore analyze the different approaches that have been developed to formulate Silymarin against various injuries and the need to administer this product in relation to the final use. Formulations such as silymarin tablets, capsules, syrup, dry syrups, drops, and solutions are available nowadays. Novel drug delivery systems containing microspheres, nanoparticles, and liposomes are currently being studied (Obeid et al., 2017). Among them, solid dosage forms form larger parts holding huge potential as they offer more benefits very quickly with improved quality of life than any other dosage forms)(Gligor et al., 2016).

Solid formulations in the form of tablets, capsules, granules, etc., do not comply with stability problems, low solubility in water, instability in pH variations, and low bioavailability, which were serious problems in the past, but the problem can be overcome by the development of technology (U. Ahmad et al., 2015). Silymarin is designed in solid preparation, and finally, solid preparation with good bioavailability is obtained (Obeid et al., 2017). The choice of solid preparation dosage form is a tablet formulation. Tablets are solid dosage forms that have advantages such as a more precise dose, better stability, ease of storage and ease of transportation, can be used for drugs with a bitter taste, and can mask the odor of the drug (Byeon et al., 2019).

The formulation of active compounds in a solid preparation dosage form is more complex than in other dosage forms because compounds are less soluble and bioavailable. In this case, the selection of properties must be

carried out on excipients that can affect the properties of silymarin solid preparations (Lim et al., 2022). Tablets can be formulated using different matrices of silymarin incorporation, such as natural or synthetic polymers, in addition to the direct compacted forms at high compression load with a maximum of 200 mg strength per tablet, as reported as the tolerated level (Cianchino et al., 2020). Using these natural or synthetic polymers either singly or in combination, effects such as disintegration time and floating lag time in dissolution tests and the deliverance rates were affected (Garg & Gupta, 2009). The excipients used were Avicel pH101, magnesium stearate, lactose, microcrystalline cellulose, and folic acid. Due to its advantages, a formulation incorporating microcystin into a tablet has achieved a twenty-fold increase in bioavailability ("Design and Development of Atenolol Matrix Tablet Employing Natural and Synthetic Polymers," 2013).

Liquid dosage forms are the most popular pharmaceutical forms. They are available in many choices such as solution, tonic, syrup, emulsion, and drops. Liquid dosage forms have advantages compared to solid dosage forms. Generally, liquid dosage forms are simple, rapid, and easy straightforward to prepare. In addition, they are easy to administer to children, the elderly, and people with dysphagia, provide better dose flexibility, and have more reliable dosing accuracy compared to solid dosage forms (M. Wang et al., 2015). They are available in alcohol solution, tincture, water solution, emulsion, suspension, liposomes, and microemulsion. The determination of silymarin dosage in the dosage form is aimed at a safe and more bioavailable dose (Busia, 2024).

Liquid dosage forms with good characteristics should be uniform, stable for a specific period of time, non-toxic, have a pleasing color and smell, have a good taste, and be easy to drink. Solutions are dosage forms prepared using a solubilizer. They have a characteristic that is not easily sedimented but can be readily decanted (Haywood & Glass, 2013). Solutions can produce a precipitation process that becomes a dispersed phase with high stability.

The stability of silymarin is influenced by pH, light, and temperature. In addition, Silymarin is easily oxidized due to exposure to air, which

produces active compounds. Without antioxidant protection, it will transform into a yellow-green form. For this reason, an induction period must be established by binding O_2 and ensuring airtight conditions (U. Ahmad et al., 2015). In addition, Silymarin has low solubility in water, which causes the compound produced to be less available for absorption by the body. To increase the solubility of the drug in a solvent, a solubilizer must be used (Kesharwani et al., 2020). The solubilizer used is a compound that can reduce interfacial tension between two phases and can spread on the surface of an immiscible solvent pair to form a homogeneous phase. These materials are usually long-chain fatty alcohols or acids. Adding ethanol to a solution can also change the cubic structure into a micelle and increase solubility (Lee et al., 2017).

Enhancing Bioavailability of Silymarin:

Bioavailability is a critical factor in therapeutic efficacy, as the inability of bioactive substances to reach the site of action in the body leads to the failure of therapeutics (Stielow et al., 2023). The very poor absolute oral bioavailability and erratic absorption of silymarin, such as free silybin A and B, are the main issues limiting its health benefits. The lower solubility of silymarin in aqueous and acidic media and its rapid enzymatic metabolism are critical factors contributing to its poor oral bioavailability (Di Costanzo & Angelico, 2019). To better understand various strategies aimed at enhancing bioavailability and efficacy, some general concepts for inceasing the therapeutic properties of drugs and nutraceuticals are discussed. In vitro and in vivo studies revealed that structural modification, complexation, nanoformulation, and micronization may enhance the solubility and bioavailability of silymarin (S. Ahmad et al., 2023). The bioavailability of silymarin is hampered mainly by its poor solubility in aqueous media, which leads to low gastrointestinal absorption (Dixit et al., 2007). Nanoformulation is a novel approach for enhancing the solubility of poorly water-soluble bioactive substances. Nanonization of bioactive substances to the nanoscale may enhance their surface contact with the gut membrane, thus improving their in vivo bioavailability (Oliveira da Silva et al., 2023). Micronization allows for the processing of smaller particles, which generally exhibit

gastrointestinal absorption (Oh et al., 1995). The nanoformulation of silymarin can enhance its water solubility, rapid gastrointestinal absorption, and, consequently, lower hepatic metabolism. Their greater circulation time in systemic circulation leads to an increase in bioavailability and a sharp drop in its dosage (Sunita et al., 2025). Thus, the development of formulations has attracted the pharmaceutical industry's attention as a further enhancement in silymarin bioavailability for improvement in its therapeutic properties. Silymarin micronization and nanoformulation show significant enhancement in its bioavailability, leading to a greater pharmacological effect at low dosage (Piazzini et al., 2019).

- **Nanoformulations:**

Nanoformulations have also gained increased attention in order to augment the bioavailability of silymarin (Y. Wang et al., 2014). Nanotechnology may be defined as the design, synthesis, characterization, and application of materials, structures, devices, and systems by controlling the shape, size, surface, and composition in the 1 to 100 nm range (Emerich & Thanos, 2003). Nano-sized drug complexes with carriers have shown potential impact in enhancing bioavailability by increasing drug solubility, protecting from degradation, limiting solubility, and reducing side effects by restricting distribution. Several materials, such as lipids, proteins, and polysaccharides, are utilized for polymeric nanoparticles (Haleem et al., 2023).

Various methodologies are available to prepare nanoformulations of silymarin, including solubilization techniques that utilize cyclodextrin or nanoemulsions, self-assembling, polymer nanoparticles, and lipid-based carriers such as liposomes, nanoemulsions, nanostructured lipid carriers, and solid lipid nanoparticles (Alshehri et al., 2022). The main promise of lipid-based approaches is that they could improve the solubility and stability of the encapsulants in a lipophilic form of the compound. Lipid-based nanoparticles might offer an appropriate aggregation of the drug molecule of silymarin to build up elevated bioavailability (Arghidash et al., 2024). An additional favorable aspect of lipids in nanoparticles is their ability to enhance the delivery of silymarin toward the naturally enhanced solubilizing

capacity of components, which was confirmed with the formation of discharge guiding. It benefits the scientific field through its modified drug biodistribution, increased drug loading, rapid onset of drug action, decrease in the dose of silymarin, and long duration of drug action (Z. Zhang et al., 2022).

Many studies have shown improvement in silymarin pharmacokinetics after its formulation as nanoparticles. In recent times, they are considered an effectively proven strategy to resolve poor solubility problems, whether in vitro or in vivo (H.-G. Choi et al., 2013). The only limitation they pose is poor stability; however, this could be resolved with optimization of the nanosuspension fabrication process, lipid dissolution method, and the lipid incorporation technique, which helps to reduce their limitations as well as enhance their practical deliverability (Poltavets et al., 2021). Despite the promising findings, several side loopholes of this approach exist, such as instability during scale-up, inappropriate scale-up requirements, limited drug loading, huge bulk mixing, controllability of drug proportions, lack of small-scale production methods and robustness, lack of batch reproducibility, and stringent regulatory hurdles (Hosseini et al., 2021). Although the preclinical studies report promising pharmacokinetic profiles, intestinal uptake, or oral delivery efficacy, this approach requires millions of dollars' worth of production plants and approved production procedures (Su et al., 2022).

- **Micronization Techniques:**

The main strategy to increase dissolution and solubility is to reduce the particle size of silymarin, considering that it is a BCS Class II drug (Javed et al., 2010). Micronization is the technique used for this purpose, and it consists of reducing the size of the particles, defining them as less than 50 µm in size. Smaller particle sizes produce an increase in the specific surface area and an increase in the dissolution rate, favoring the solubility and bioavailability of Silymarin (Noor & B.H. Al-Khedairy, 2019). Currently, several investigations focus on these lines. There are many methods available to reduce particle size through micronization, such as solid precipitation, supercritical processes, electro spraying, shearing or attrition, and grinding techniques such as jet milling, ball milling, and spray drying, in

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addition to using polymers and carriers for pharmaceutical formulations (Vandana et al., 2014).

This review mainly deals with micronization techniques for silymarin, where several methods can be used to carry out this process to reduce the particle size of Silymarin. The most common include jet milling, a very effective method leading to a 20-time reduction in particle size, and ball milling, one of the most researched (Borhan et al., 2013). Jet milling uses superheated air to atomize the feedstock into micron-size particulates by means of gas turbulence in the milling nozzles and meeting the criteria for particle size distribution (W. S. Choi et al., 2004). It was found that jet milling silymarin from 186 to 25 µm yields only 30% residual crystalline content compared to the original drug. Testing jet milling on a Silymarin mixture with CNC (in a 1:1 and 1:3 w/w ratio) showed a slight increment in micronization efficiency for Silymarin and mixed samples, where the rational size was around 7 µm. The fine particles were found to fly by air out of the ball milling chamber and to be carried by the carrier air (Noor & B.H. Al-Khedairy, 2019)(Sher et al., 2023).

- **Bioenhancers and Absorption Enhancers**

The term bioenhancer is used for substances that augment the absorption of nutrients and drugs. In the broader sense, absorption enhancers and bioavailability enhancers are considered analogous to bioenhancers (Chivte et al., 2019). Research has been conducted on the bioenhancing properties of some bioflavonoids like naringenin and quercetin for the past couple of years (Bhimanwar et al., 2020).

Bioenhancing properties exist in the likes of Omega 3, Vitamin D, and other nutrients. Efforts had been made to enhance the absorption of some expensive drugs so as to reduce the dose and toxicity (Thorat et al., 2023). In terms of levels of acceptance and commercial feasibility, bioenhancing properties of drugs and nutraceuticals have gained more momentum than the bioenhancing properties of herbal drugs (Peterson et al., 2019). A number of natural and synthetic substances can enhance the absorption of drugs. The important bioenhancing candidate substances are bergaptene and piperine (S, 2021). Combination therapies with bioenhancers and silymarin have shown

an increased bioavailability of silybin. In the last couple of years, there have been reports on various emerging patented products for improved pharmacokinetics through enhanced absorption. This could be through the use of biojunctors and bioenhancers (Javed et al., 2022). Absorption through bioenhancers could limit first-pass metabolism, thus increasing the systemic availability of the drug and hence the therapeutic benefits of the currently developed formulation of silymarin (Javed et al., 2018). However, regulatory considerations will limit their use in the formulation for commercial products.

Several promising technologies may enhance the bioavailability of silymarin and address the associated challenges in the future. The integrity of silymarin during degradation can be protected by using liposomes or nanoliposomes, which can significantly enhance the delivery of silymarin towards the target tissue. One such approach is liposomal encapsulation, which helps to overcome the solubility issue and helps in release control, further aiding in minimizing the effect of first-pass metabolism (Kumar et al., 2014). Sublingual and Buccal Formulation: The silymarin formulations administered sublingual/buccal could permit the efficient absorption of the active components in the mouth mucous membranes without experiencing first-pass metabolism (El-Samaligy et al., 2006). Spray Dry Technology: This technology is very useful in case of oral and topical nearness of medication, where silymarin powders can be soaked up to a great part as compared to before in light of the fact that they are an expansive part regarding size and dissolvability (Sansone et al., 2018).

Regulatory Considerations in the Development of Silymarin Products: Achieving success in silymarin-based products also means addressing a complex web of regulations that varies according to the intended use—dietary supplement, pharmaceutical drug, or cosmetic product. In the USA and Europe, silymarin fits the legal definition of both. The FDA, EMA, and other global authorities have established regulations necessary for companies to produce effective and safe silymarin products and meet regulatory requirements from labeling to preferably using good manufacturing practices (Klut, 2022). As a dietary supplement, silymarin is regulated so

that companies can market the product with no pre-market approval process, so long as the product is manufactured in accordance with Good Manufacturing Practices (GMP) and is properly labeled (Fenclova et al., 2019).

For therapeutic purposes, silymarin would have to go through the same clinical trials and regulatory process, including New Drug Applications (NDA), to prove it is safe and effective at treating a specific condition. As for cosmetics, silymarin must be safe for use, and any claims for its skin benefits cannot include medicinal uses without proper approval. Rigorous toxicology studies, clinical trials, and quality assurance processes are therefore essential to guarantee the safety and quality of silymarin products (Clarridge et al., 2022).

Adequate reporting of adverse events and post-market surveillance are also important for monitoring the longer-term safety of products in the market, along with having mechanisms for product recalls, where appropriate. Moreover, the trend towards sustainability and transparency in manufacturing means that brands can further improve their positioning by committing to sustainable sourcing and eco-friendly practices, as consumers increasingly consider the ethics of their consumption (Choudhury et al., 2023).

Moreover, firms may pursue patent protection for novel formulations or delivery mechanisms, providing them with market exclusivity and a competitive advantage. Companies can ensure that their silymarin products meet regulatory requirements by addressing all these regulatory considerations: clinical validation and labeling, manufacturing, and post-market safety—ensuring consumer safety and trust. Adhering so carefully to regulations will not only ensure seamless entry into the market, but it will also play a role in the sustainable and ethical transition of silymarin-based products into the international market.

Market Trends and Commercialization Opportunities:

The majority of silymarin-based pharmaceutical products are sold in clinics because people with liver diseases like cirrhosis, hepatitis, and fatty liver disease need them so much. This is expected to drive segment growth.

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Individuals seeking general wellness supplements offer significant opportunities for silymarin-based product providers. The target consumers range from older adults at high risk for liver diseases to younger, health-conscious patients. Considered by the global liver disease treatment market with an expected increase due to the increasing needs for herbal and natural products, it makes silymarin a profitable player in the health and well-being market (Bahmani et al., 2015).

The global silymarin market was estimated at around USD 98.7 million in 2024 and is expected to reach USD 101.85 million by 2025, mounting at a compound annual growth rate (CAGR) of 3.2%. Likewise, the global milk thistle product market, to which silymarin belongs, is anticipated to grow from USD 1.63 billion in 2024 to USD 3.81 billion by 2034, at a CAGR of 8.88%. People are becoming more aware of possible liver problems and are also interested in natural solutions. This is likely to lead to the growth of the silymarin market, which is supported by major market players and distribution channels like online stores, pharmacies, and health stores (Jadhav et al., 2020)(Bhattacharjee et al., 2023).

There are a variety of potential business opportunities surrounding the commercialization of silymarin, which has recently been gained recognition as a potent, natural therapy. With growing consumer demand for natural and plant-based ingredients, silymarin stands to take a sizeable share in the nutraceuticals and functional foods sectors.

Its diverse uses in liver health, detoxification, skin care, and cognitive protection make it a multi-faceted product portfolio that appeals to a wide range of consumer segments. Education-based marketing should inform them about the antioxidant, anti-inflammatory, and hepatoprotective benefits of silymarin (Hellerbrand et al., 2017). It could be marketed within a context that refers to its natural source that explains its biopharmaceutical properties, making it attractive to health-minded consumers who are seeking out safe, effective, and natural alternatives to manufactured pharmaceuticals (Himmatul Miftah et al., 2020).

Brand differentiation will be an important factor in a crowded market. Investments in sustainable and ethical sourcing practices for silymarin will

resonate specially with eco-conscious consumers. Sustainable packaging and where your products come from should resonate with consumers because they care about the environment(Odubo et al., 2024).

Personalized health is another strong marketing angle for silymarin and the advancements in genetic testing and personalized nutrition; the marketing of silymarin-based products as a part of tailored health solutions could prove to be a lucrative niche. By highlighting how silymarin may be tailored to a certain genetic profile or disease (e.g., liver disease, metabolic syndrome, or even neurodegenerative disease), companies can provide personalized health routines, thereby increasing consumers' engagement and confidence (Elateeq et al., 2020).

To successfully commercialize silymarin, we will also need to form strategic partnerships with established contributors in the pharmaceutical, supplement, and beauty markets. For instance, partnerships with clinical researchers could lead to the verification of silymarin therapy in liver disorders, metabolic disease, and even cancer therapy. Working together with cosmetics companies could lead to new and exciting skin care products, and working together with supplement companies could lead to new, highly targeted products containing silymarin for liver health, anti-aging, or cognitive support (Saggar et al., 2022).

Fired up by a more social perspective on the concept of health and the broader view on preventive health care, social media is the marketing channel of choice that companies can look to exploit to reach both health-conscious patients and those in need of preventive health care solutions. The publication of educational content, user testimonials, and clinical studies demonstrating the efficacy of silymarin would help establish credibility and generate more consumer sales (Ayu et al., 2022).

Conclusion:

Silymarin has the potential to be a great therapeutic agent, particularly in liver diseases; however, the advancement of extraction methods, improving bioavailability, and development of novel formulations are the main ways for its full potential in the pharmaceutical industry. Further studies should also aim at increasing extraction efficiency using modern

practices, modifications for drug delivery systems such as nanoparticles, liposomes, and solid lipid nanoparticles, and an investigation of pharmacokinetics for absorption and distribution comprehension in humans. Moreover, extending its clinical applications to other therapeutic contexts, including neurodegenerative diseases, diabetes, cancer, and cardiovascular health, will be vital for the emergence of its broader medicinal applications. Future studies could explore drug combinations, particularly with other hepatoprotective or anticancer agents, which may provide a synergistic therapeutic advantage for silymarin. Commercial potentials exist in developing innovative, consumer-acceptable formulations such as sustained-release tablets, functional foods, etc., and entering into emerging markets where the consumer is inclined towards natural and botanical products. This would also help broaden its use in clinical and market markets by securing regulatory approvals for these new uses. Moreover, by prioritizing sustainable sourcing and ethical extraction practices, we would actively combat environmental damage, enhance the reliability of the supply chain, and align with the increasing consumer preference for sustainable products, ensuring the long-term success of silymarin in clinical settings and positioning it as a significant contributor to the global natural health products market as a more sustainable choice.

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