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Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2021.v13.i01.pp21-30

HEPATOPROTECTIVE EFFECT OF SILYMARIN-LOADED NANOPARTICLES IN CARBON TETRACHLORIDE-INDUCED HEPATOTOXICITY

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Article info

Received date:20-08-2020
Accepted date:16-11-2020
Published date:21-03-2021
ISSN;0975-8216

Keywords:

Silymarin, Nanoparticles, Hepatoprotection, Carbon tetrachloride, Oxidative stress

Abstract

Silymarin, the flavonolignan extract of milk thistle, is widely used as a liver-supportive agent, but its poor solubility and low oral bioavailability limit exposure. This review summarises published work on nanoparticle and related carrier formulations of silymarin in carbon tetrachloride hepatotoxicity, the standard rodent model of radical-mediated liver injury. It outlines the toxicological mechanism, the pharmacokinetic problems of free silymarin, the main formulation strategies and the biochemical, oxidative and histological effects reported by others. Evidence suggests improved protection per dose with nanoformulations, but studies are small, comparators vary and reporting is incomplete. No new experimental data are presented.

1. INTRODUCTION

The liver takes the first hit from almost everything swallowed, whether it is a prescribed drug, an industrial solvent or a mouthful of alcohol. Damage can stay quiet for years and then arrive suddenly, and the treatments on offer for toxic and fatty liver disease are still limited. Silymarin, the flavonolignan-rich extract of milk thistle (*Silybum marianum*), is one of the oldest herbal products used for liver complaints and is sold in most parts of the world as a supportive agent [1, 2]. Its main constituent, silybin, has been examined for antioxidant, anti-inflammatory and antifibrotic actions for

several decades, and the literature on it is large, uneven in quality and often enthusiastic beyond what the data allow [3, 4].

Yet silymarin is an awkward molecule to work with. It dissolves poorly in water, is absorbed unpredictably from the gut and is cleared quickly after conjugation, so the plasma concentrations reached with ordinary oral products are low and variable [5, 6]. Formulators have therefore tried phospholipid complexes, liposomes, self-emulsifying systems and, more recently, polymeric and solid nanoparticles, all with the same aim of raising exposure in the target organ without raising the dose [7, 8, 9, 10]. Whether this effort has produced protection that is convincingly better than the plain extract is the question this review keeps returning to.

The practical importance of the problem is easy to state. Drug-induced liver injury is a leading reason for withdrawal of medicines and a frequent cause of acute liver failure, and chronic exposure to alcohol, viruses and metabolic stress produces a large burden of fibrosis and cirrhosis worldwide [11, 12]. Any agent that offered even modest protection at low cost would be welcome, which partly explains the sustained enthusiasm for silymarin and the effort put into improving it. The difficulty lies in turning a plausible laboratory effect into a result that survives a properly designed trial.

This review covers what has been published on silymarin-loaded nanoparticles in carbon tetrachloride (CCl_4) hepatotoxicity, the most widely used chemical model of acute and chronic liver injury in rodents [12, 13]. It is a narrative synthesis of work by other groups and reports no new experimental data. The sections that follow describe the model, the problems with free silymarin, the nanoparticle approaches, the protective effects reported, and the gaps that limit translation to patients. Where the evidence rests on a single laboratory or on small groups, the text says so rather than smoothing the difference.

Silymarin has a long record of use. Preparations from milk thistle fruit have been used in Europe for liver and gall bladder disorders for centuries, and standardised extracts became widely available in the twentieth century [1, 3]. Interest in nanoparticle delivery is much more recent and follows a general pattern in natural product research, in which a compound with credible activity and poor pharmaceutical properties is repackaged in the hope of unlocking its potential [14]. The pattern is productive, but it requires care that gains in measured exposure are not simply reported as gains in benefit.

Clinical results for silymarin itself have been inconsistent. Systematic reviews found little convincing benefit on mortality in alcoholic or viral liver disease, and a randomised trial in chronic hepatitis C patients who had failed interferon therapy did not show a significant gain over placebo at the doses tested [15, 16]. These findings are part of the reason formulation work matters. A weak clinical signal may partly reflect weak exposure rather than an inactive compound, although that remains a hypothesis and not a demonstrated fact. Reviews written by sympathetic authors have tended to emphasise the experimental positives, so the clinical record is a useful corrective [17, 18].

2. THE CARBON TETRACHLORIDE MODEL

Carbon tetrachloride is activated in hepatocytes by cytochrome P450 enzymes, chiefly CYP2E1, to the trichloromethyl radical. This radical attacks membrane phospholipids and, in the presence of oxygen, forms the trichloromethylperoxyl radical, which starts lipid peroxidation and damages the endoplasmic reticulum within minutes [12, 19]. Centrilobular necrosis, fatty change and a rise in serum transaminases follow, with the zone around the central vein affected first because that is where P450 activity is highest. The mechanism explains why the model is so sensitive to antioxidants and why it has been used to screen so many plant extracts.

Dosing schedules differ widely between laboratories. A single intraperitoneal or oral dose gives acute injury that peaks within one to two days, while repeated doses over several weeks produce fibrosis, with activation of hepatic stellate cells and deposition of collagen in the perisinusoidal

space [11, 20]. The vehicle (often olive or corn oil), the route, the strain and the sex of the animals all alter the severity of injury. That is one reason numerical results from different laboratories are hard to compare, and why a formulation that looks superior in one paper may look merely equal in another [13].

Standard read-outs are fairly consistent across papers. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities are usually measured with colorimetric methods of the Reitman–Frankel type, alkaline phosphatase and bilirubin supply supporting evidence, and hepatic malondialdehyde (MDA, by the thiobarbituric acid reaction) and reduced glutathione (GSH) indicate oxidative burden [21, 22]. Histology, scored for necrosis and inflammation or for fibrosis, remains the anchor against which biochemical changes are judged. A paper that reports enzymes without histology, or the reverse, leaves the reader with only half of the picture. Ethical and practical considerations also shape the model. Carbon tetrachloride studies cause pain and distress of a significant degree in the acute phase, so refinement through humane end points, minimal group sizes and good experimental design is expected, and alternative approaches with human liver spheroids or precision-cut slices are increasingly discussed [13, 23]. Such systems capture only parts of the response, notably hepatocyte injury, and cannot yet replace whole-animal work for questions about absorption and distribution, which are central to nanoparticle formulations.

The model has limits that matter when interpreting protective claims. Carbon tetrachloride injury is toxic and radical-driven, so it says little about immune-mediated, metabolic or cholestatic disease. An antioxidant that looks excellent here may do nothing in non-alcoholic steatohepatitis, where the injury sequence is different. Spontaneous recovery is also quick after a single dose, so the timing of treatment relative to the toxin must be stated clearly, and a compound given before the toxin is being tested as a preventive, not as a treatment [12, 20].

3. SILYMARIN AND ITS DELIVERY PROBLEM

Silymarin is a mixture rather than a single compound. The silybin diastereomers (A and B) dominate, accompanied by isosilybin, silychristin, silydianin and the flavonoid taxifolin, and the proportions vary between plant batches and extraction methods [2, 3]. This variability affects reproducibility in animal work, since two papers that both say "silymarin" may in fact have dosed different mixtures. Standardisation to a stated silybin content is common in the better papers but is not universal, and it should be treated as a minimum requirement before any comparison of formulations is believed.

Chemistry gives some reason for caution in reading the antioxidant claims. Silybin is a flavonolignan with phenolic hydroxyl groups that can donate hydrogen to radicals in a test tube, but cellular and in vivo antioxidant effects often depend on indirect routes, including induction of endogenous defences, rather than direct scavenging [4, 24]. In a test tube the compound can also act as a pro-oxidant under some conditions. This matters for formulation because a delivery system that raises tissue concentration may change the balance between these actions, and the dose-response relationship is therefore not necessarily linear or monotonic.

Several actions have been proposed for its liver effects. It scavenges free radicals, inhibits lipid peroxidation, supports glutathione levels and stabilises hepatocyte membranes. It also reduces nuclear factor kappa B signalling and the release of inflammatory cytokines, and it dampens stellate cell activation in fibrosis models [24, 25, 26]. Which of these actions drives protection in a given experiment is rarely resolved. Doses used in rodents are also often well above those humans could reach, so a mechanism shown at a high concentration in a dish or a high dose in an animal may not operate at a clinical exposure.

Analytical methods deserve more attention than they usually receive. Reversed-phase high-performance liquid chromatography with ultraviolet or mass spectrometric detection is the standard route to quantify silybin A and B, isosilybin and the other

flavonolignans in extracts and in plasma, and sample preparation must include enzymatic deconjugation if total rather than free concentrations are wanted [2, 5]. Studies that report only "silymarin" by an ultraviolet absorbance method may be measuring a mixture of interfering flavonoids. Differences in assay therefore account for some of the disparity in reported bioavailability gains between papers.

Pharmacokinetic data explain the interest in formulation. After an oral dose of a standard extract in volunteers, free flavonolignans are barely detectable and most of the circulating material is glucuronide and sulphate conjugates, with short half-lives [5]. Silymarin has been described as a poorly soluble compound with limited intestinal permeability, and food and bile secretion influence its uptake [6, 27]. Bioavailability gains of several-fold have been claimed for phospholipid complexes and lipid systems, though most comparisons involve a handful of animals or volunteers and use different analytical methods, which makes ranking the approaches difficult [7, 9].

Extrapolating doses from rodents to people is another source of confusion. Conversion by body surface area, which is the usual approach, reduces a rodent dose of several hundred milligrams per kilogram to a lower human equivalent, yet even this can exceed the amounts in ordinary supplements [17, 18]. Some authors present protective effects at a dose that, once converted, falls within clinical use, and others work far above it. Readers should check which case applies before assuming a result is relevant to practice, and formulation papers could help by stating the conversion explicitly.

Interaction potential is a secondary concern. Silymarin constituents inhibit some cytochrome P450 and conjugating enzymes in vitro, and the interaction literature suggests the effect is generally modest at ordinary doses [27]. A nanoparticle that raises exposure could in principle shift this balance, particularly for narrow-therapeutic-index drugs handled by the same enzymes. Interaction work should therefore accompany any new formulation intended for human use, and not be left to post-marketing reports. At present almost none of the nanoparticle papers address the question at all.

4. NANOPARTICLE APPROACHES

Polymer-based carriers are the most common platform. Poly(lactic-co-glycolic acid) and related biodegradable polymers can entrap lipophilic compounds, release them slowly and be made with solvent-evaporation or nanoprecipitation methods, giving particles of roughly 100 to 300 nm [28, 29, 30]. Lipid-based systems, liposomes and self-microemulsifying drug delivery systems (SMEDDS) follow a different logic: they keep the drug in solution through the gut and may make use of lymphatic transport, which bypasses part of the first-pass loss [8, 9]. Each approach trades simplicity against stability, and there is no agreement on which suits silymarin best.

Solid nanoparticles of silymarin itself, prepared with stabilisers and without a polymer matrix, were reported to give a markedly higher dissolution rate and plasma exposure than the raw extract in rats [10]. The attraction is a high drug load and a simple composition, which matters because carrier-heavy particles may carry only a few per cent of active ingredient by weight. Surface charge, particle size and polydispersity are the characteristics most often reported, along with entrapment efficiency where a carrier is used [28, 30]. Release profiles are usually measured in simple buffers that say little about behaviour in the gut.

Why would particles help the liver in particular? Particles in the lower hundreds of nanometres are cleared substantially by the mononuclear phagocyte system, and the liver, with its fenestrated sinusoids and abundant Kupffer cells, takes up a large share of an intravenous dose [31, 32]. Passive accumulation of this kind is useful for a hepatoprotective agent but is not selective for hepatocytes, and surface ligands for hepatocyte or stellate cell targeting remain largely experimental [33]. For oral products the argument is different, since the main gain is absorption and not organ targeting, and the two effects are often conflated in the discussion sections of papers.

The choice of stabiliser or carrier carries consequences beyond particle size. Surfactants such as polysorbates or poloxamers, polymers such as polyvinyl alcohol and lipids from soy or egg each have their own tolerance, irritation and regulatory profile, and some have been associated with hypersensitivity or with effects on membrane transporters [29, 30]. In rodent studies, the control group should therefore receive blank particles containing the same excipients, to separate the effect of the carrier from that of the drug. Such blank-particle controls are included in only part of the CCl_4 literature on silymarin, and their absence weakens the attribution of benefit to the loaded drug.

Characterisation deserves its own mention because it decides whether results can be repeated. Particle size by dynamic light scattering, zeta potential, morphology by electron microscopy, drug content by validated chromatography and in vitro release are the usual set, and the better studies add stability under storage and in simulated gastric and intestinal fluids [28, 29]. Because silymarin is a mixture, the assay should quantify several flavonolignans and not only silybin, otherwise changes in composition during processing can pass unnoticed [2].

Evidence from published studies using silymarin-containing formulations in CCl_4 injury and in related pharmacokinetic work is brought together in table 1. Most studies compare the formulation with free silymarin at an equal or lower dose and with a vehicle control, and report transaminases, oxidative markers and histology. The grouping of the entries by type of evidence is shown in fig. 1. The table is deliberately qualitative, because absolute values depend on the toxin dose, the strain and the assay, and cannot be pooled across papers.

Table 1: Published findings on silymarin formulations and carbon tetrachloride liver injury

Topic	Reported finding or feature	Ref.
Silymarin botanical extract	Mixture of silybin, isosilybin, silychristin and silydianin; composition varies with source and extraction.	[2, 3]
Oral extract human plasma	Mostly conjugated flavonolignans with very low free levels after oral dosing.	[5]
Standard dosing CCl4 rodent	Reduced transaminases and lipid peroxidation, but dose levels are high compared with human use.	[24, 26]
Phospholipid complex silybin	Higher plasma exposure than unformulated silybin in rats.	[7]
Buccal liposomes silymarin	Improved bioavailability reported through a liposomal route avoiding first-pass loss.	[8]
SMEDDS silymarin	Self-emulsifying system improved dissolution and absorption compared with the raw extract.	[9]
Solid nanoparticles silymarin	Greater hepatic protection and exposure than raw silymarin in injured rats.	[10]
PLGA particles general carrier	Sustained release of lipophilic drugs with controllable size; liver uptake is substantial.	[28, 30]
Liver uptake nanoparticles	Kupffer cell and sinusoidal uptake explains accumulation but limits hepatocyte selectivity.	[31, 32]
Chronic fibrosis stellate cells	Reduced collagen deposition and stellate cell activation reported with silymarin treatment.	[11, 25]
Clinical trials hepatitis C	No significant benefit over placebo with standard oral extract in interferon failures.	[15, 16]

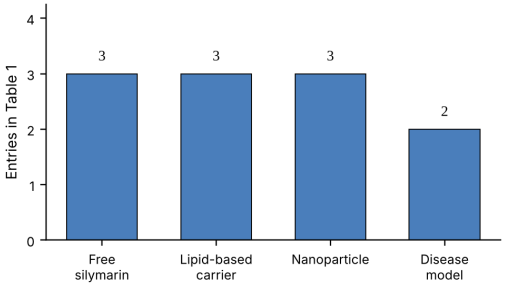


Fig. 1: Number of entries in table 1 by formulation and evidence category

Scaling of production also decides whether the better systems are worth developing. Nanoprecipitation and high-pressure

homogenisation are generally scalable, whereas some emulsion-solvent methods with large volumes of organic solvent are not, and the cost of polymers such as PLGA is high relative to a low-cost botanical extract [28, 30]. A formulation that adds a large cost to a product sold on price will find a market only if the clinical gain is clear, which returns the discussion to the need for human data. Cheaper routes, such as phytosome-type complexes made with food-grade phospholipids, may therefore stay ahead commercially even if nanoparticles win in the laboratory [6, 7]. Without head-to-head data, neither side of that argument can be settled, and cost-effectiveness is rarely discussed.

Route of administration shapes what the particles are expected to do. Oral dosing relies on improved dissolution, mucus penetration and uptake, whereas intravenous or intraperitoneal dosing bypasses the gut and tests distribution and cellular uptake instead [31, 32]. Many silymarin studies in CCl_4 injury use the oral route in rodents by gavage, which is also the only route likely to be accepted for a supportive product. Parenteral comparisons are interesting for mechanism but say less about whether a tablet or capsule could ever perform in the same way.

Manufacturing detail receives little attention in the biological papers. Residual organic solvent, batch-to-batch reproducibility of particle size and storage stability are seldom reported, though they decide whether any laboratory result could become a product [28, 29]. Scale-up from a few millilitres in a research laboratory to a validated process is a separate engineering problem, and polymer cost and regulatory status of excipients also shape which platforms can realistically reach patients.

5. REPORTED HEPATOPROTECTIVE EFFECTS

In acute CCl_4 models the typical finding is that pretreatment or concurrent treatment with silymarin nanoparticles lowers serum alanine and aspartate aminotransferase more than the same dose of free silymarin, often bringing values closer to those of untreated controls [10]. Liposomal and phospholipid-based systems report similar directional changes in pharmacokinetic and tissue measures, though not always in the CCl_4 setting [7, 8]. The size of the difference between free and formulated silymarin varies, and in some reports it is clear mainly at the lower end of the dose range.

Not every comparison favours the new formulation. In some reports free silymarin at a high dose protected nearly as well as a nanoparticle at a lower dose, and differences in histology scores did not reach conventional significance even where enzyme changes did [10, 26]. Publication bias probably favours the positive findings, as it does throughout preclinical research. A reader looking at the whole literature should expect that some negative or neutral results never appeared, and should treat the apparent consistency of benefit with a degree of scepticism proportionate to the small number of independent groups involved.

Oxidative markers move in the expected direction. Hepatic malondialdehyde falls, and reduced glutathione and the activities of superoxide dismutase and catalase are partly restored compared with the toxin-only group [24, 26]. Histology tells the same story, with less centrilobular necrosis, fewer ballooned cells and a reduced inflammatory infiltrate. These effects are what one would predict from better delivery of a known antioxidant, which makes the consistency reassuring but not very surprising. It also means that the findings do not discriminate between improved delivery and some additional effect of the carrier.

Animal factors matter more than they are given credit for. Male rodents generally show greater susceptibility to carbon tetrachloride than females, mouse strains differ in CYP2E1 activity and fibrogenic response, and diet, fasting state and housing influence both toxin metabolism and antioxidant status [12, 13]. When a paper tests a formulation in one sex of one strain, the finding is a starting point. Replication across strains, or at least an explicit statement of the limitation, would make the protective claims easier to weigh against one another.

Chronic dosing studies are fewer. Where silymarin has been given over several weeks

of CCl_4 exposure, reductions in collagen deposition and in markers of stellate cell activation have been described, in line with older work on the free extract [11, 20, 25]. Whether nanoformulations give an additional antifibrotic benefit beyond a higher plasma level is not clear from the literature, since few studies compare groups at equal exposure. Fibrosis is also slow to reverse, and a delay between the last toxin dose and tissue collection can change the result considerably.

Dose comparisons deserve some care. A formulation that works at half the dose of free silymarin is a useful result, but only if the control group received the same preparation of extract and the same vehicle. Several reports compare against suspensions in carboxymethylcellulose without stating the particle size of the control, which can exaggerate apparent advantages, since a coarse suspension of a poorly soluble powder is a weak comparator [10]. A fairer design would add a phospholipid complex or a simple solubilised preparation as a second reference.

Mechanistic end points add depth when they are present. Some studies report reduced tumour necrosis factor alpha and interleukin 6 in liver tissue, lower expression of fibrogenic mediators such as transforming growth factor beta, and fewer apoptotic hepatocytes, all consistent with the anti-inflammatory profile described for free silymarin [24, 25]. Others point to activation of the Nrf2 antioxidant response. These findings are plausible, yet most are single measurements in small groups, and they establish association with protection rather than cause. Carrier-only control groups are needed to show that the particle itself is not contributing, and they are included in only some papers.

Comparisons across delivery systems are scarce, which is a real gap. A phospholipid complex, a liposome, a self-emulsifying system and a polymeric nanoparticle have each been compared with plain silymarin, but almost never with one another in the same hands under the same conditions [7, 8, 9, 10]. Reading across papers, the improvement over the raw extract looks broadly similar in direction, yet it differs in size and cannot be ranked. A head-to-head study at equal silybin dose, using one toxin schedule and one analytical method, would settle more than another single-system report.

Beyond carbon tetrachloride, silymarin has been examined against paracetamol, thioacetamide and alcohol-related injury, and a veterinary literature on milk thistle derivatives has accumulated [17, 34]. These studies suggest the protective profile is not unique to one toxin, though formulation data are thinner in those models and the mechanisms of injury differ from the radical pathway seen with carbon tetrachloride. A reasonable summary of the preclinical position is that nanoformulation improves the protection obtained per unit dose of silymarin in rodent CCl_4 injury, that the biochemical, oxidative and histological end points agree with each other, and that the magnitude of improvement depends heavily on the comparator used [10, 18]. This is a worthwhile finding, yet it is a long way from showing that patients would gain, and the two should not be confused in discussion sections.

6. SAFETY, TRANSLATION AND GAPS

Silymarin has an excellent safety record in people, with mild gastrointestinal effects and occasional allergic reactions the main complaints [17, 18]. Nanoformulations change that picture only partly. Excipients, residual solvents and the particle itself need their own toxicity assessment, and acute oral toxicity testing along the lines of OECD guideline 423 is a minimum before wider use [35]. Repeated-dose studies that look at liver, spleen and kidney would be sensible too, because particles that accumulate in macrophages may persist longer than the drug they carry [31].

Regulatory status shapes what evidence will eventually be asked for. In many markets silymarin is sold as a dietary supplement or traditional herbal medicine, where claims are modest and quality expectations lower, whereas a nanoformulation presented as a medicine for liver disease would be assessed as a new product, with full quality, nonclinical and clinical documentation [35, 36]. The step from supplement to drug is large, and it is one reason the many encouraging rodent papers have not been

followed by trials. A development plan would need to decide early which route it intends to take, since the choice determines how much of the existing literature can be relied upon.

Study design is the weakest part of the evidence. Many reports use small groups, do not describe randomisation or blinding, and give limited information on how histology was scored. Guidance on the design and reporting of animal experiments asks for precisely these details, and adherence in this literature appears patchy [13]. Without such detail, effect sizes are difficult to trust. Pathologists scoring slides without knowing the group allocation would remove an obvious source of bias at almost no cost, yet few papers state that this was done.

Stability is a practical hurdle that laboratory papers seldom address. Nanosuspensions and lipid systems can aggregate, undergo Ostwald ripening or lose entrapped drug over weeks, and polymeric particles may hydrolyse in storage. Formal stability testing follows the ICH Q1A(R2) approach, with defined temperature and humidity conditions and time points, and it is expected for any product that moves beyond the bench [36]. Freeze-drying with a cryoprotectant is a common remedy for aqueous dispersions, and it should be demonstrated that particle size is restored on reconstitution, since a redispersion that clumps would undo the formulation advantage.

Clinical trial design for a formulated product would also need thought. Candidate populations include patients with drug-induced liver injury, alcohol-related disease or fatty liver, in whom oxidative stress is believed to contribute, and the end points would have to go beyond enzyme changes to histology or validated non-invasive fibrosis scores [11, 17]. Because aminotransferases fall spontaneously when exposure stops, short uncontrolled studies are easy to misread. Placebo-controlled designs of adequate duration, with exposure measured in at least a subset of participants, would help to separate a formulation effect from natural recovery.

There is also a mismatch of end points. Carbon tetrachloride studies measure protection when the drug is given before or with the toxin, while patients present after injury has begun. Therapeutic designs, in which treatment starts after the insult, would be closer to practice. Likewise, the human trials of silymarin that disappointed used oral extracts without enhanced bioavailability, so a properly powered trial of an optimised formulation has not yet been done [15, 16]. Until it is, claims about clinical benefit from nanoparticles are extrapolations.

Quality of the plant material connects safety to efficacy. Herbal extracts vary with growing conditions, harvest time and extraction solvent, and a milk thistle product sold as a supplement may contain well below the labelled amount of silybin. Veterinary and human studies of milk thistle derivatives have both noted this problem [4, 34]. A nanoformulation built on a poorly defined starting extract inherits its variability, so pharmacopoeial-style specifications for the raw material, with a defined flavonolignan profile and limits for contaminants, belong in any development plan. Future work could usefully report full particle characterisation, compare formulations at matched plasma or tissue exposure, include a phospholipid-complex comparator rather than only the raw extract, and measure liver concentrations directly. Hepatocyte targeting remains an attractive idea but needs convincing evidence that selectivity improves outcome and not just uptake [31, 32, 33]. Independent replication would help most, since much of the nanoparticle evidence comes from single laboratories and from a few formulation types.

7. CONCLUSION

Published work gives a coherent, if modest, picture. Silymarin is a mixture of antioxidant flavonolignans that protects the liver in carbon tetrachloride models, but standard oral products deliver little free compound to the blood. Nanoparticles, liposomes, phospholipid complexes and self-emulsifying systems raise exposure, and in the few studies that tested them against CCl_4 they improved enzyme, oxidative and histological end points beyond those of the raw extract [7, 8, 9, 10]. The direction of the effect is consistent across end points, which is reassuring.

The strength of that conclusion is limited by small groups, uneven reporting and comparators that are not always matched. Human trials of ordinary silymarin have been unconvincing, and no trial has yet tested an optimised formulation [15, 16]. Future studies should follow reporting standards, test treatment after injury, measure tissue exposure and include safety work on the carrier itself [35]. Until then the preclinical case remains encouraging rather than settled, and any claim of clinical benefit from silymarin nanoparticles should be held as a hypothesis awaiting proper trials.

8. ABBREVIATIONS

ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, CCl_4-Carbon tetrachloride, CYP-Cytochrome P450, GSH-Reduced glutathione, MDA-Malondialdehyde, PLGA-Poly(lactic-co-glycolic acid), SMEDDS-Self-microemulsifying drug delivery system, OECD-Organisation for Economic Co-operation and Development

9. FUNDING

Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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