NOVEL FORMULATION APPROCHES FOR GLYCOSIDES

ARTICLE REVIEW

Submitted by

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CERTIFICATE

This to certify that the research work in thesis entitled **"Novel Formulation approaches for Glycosides "** submitted to the Faculty of Pharmacy, Tishk International University, Erbil, Iraq, in partial fulfillment of the award of degree of Bachelor of Pharmacy, and the research has been carried out during academic session of 2022-2023 by "**Bawan Jalal Abdullah, , Kale Bahadeen Othman, and Kochi Ari Ibrahim"** Under the supervision of **Dr. Rozhan Arif** and **Dr. Omji Porwal**.

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Abstract

Background: In our research we focused on Garcinia, Sennosides, Chrysophanol and Paclitaxel. The reason behind why we selected these plants was due to their unique and paramount effects and features such as (antineoplastic, antibacterial, antioxidant and hepatoprotective) activities.

Objectives: The aim of our study was to review many different research papers to relate them and differentiate between them, in other words to find similarities and differences in all methods to conclude which methods are considered advantageous over others, and what can be implemented now to provide optimal formulations. Also, for flourishing our knowledge as undergraduate students to be aware of different techniques to isolate as well as formulate plant derivatives.

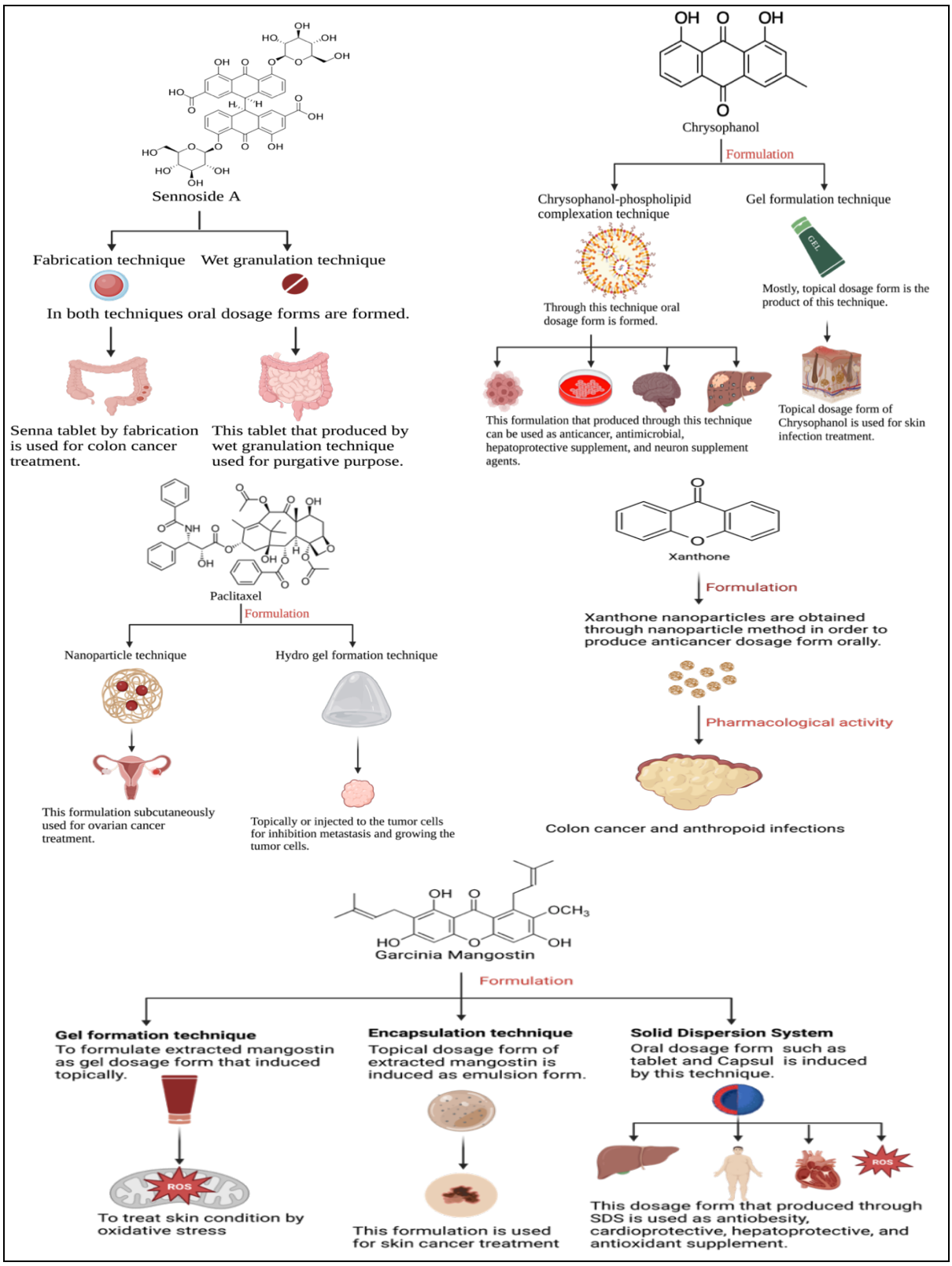
Methods: Several techniques have been employed to improve and increase the absorption and bioavailability of these types of glycosides that were mentioned. Among them, solid gel formation, encapsulation, wet tablet granulation, and fabrication methods are utilized to formulate the Garcinia and sennoside glycosides. Other types of glycosides like Chrysophanol and Paclitaxel are formulated by hydrogel preparation, complexation of phospholipids with Chrysophanol, nanoparticle technique, and gel formulation for Paclitaxel.

Results: The bioavailability of the specific drugs were increased and the safest technique to formulate them were found.

Conclusion: different methods and new flourishing results were reviewed, compared and evaluated.

Keywords: Garcinia glycoside, Sennoside glycoside, Paclitaxel, Chrysophanol, formulation, solubility, bioavailability.

Graphical abstract



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List of abbreviations and symbols

10-DAB-III.	10-deacetyldabacin-III
3T3-L1.	3-days transfer, inoculum 3x10,00000 cells.
AST.	Aspartate aminotransferase enzyme
ATCC.	American-type culture collection
C57BL/6.	C57 black 6
CMC	Critical micelle concentration
CPC	Corytophanid-phospholipid complex
CTAB.	Cetrimonium bromide
CVS.	Cardiovascular system
DMF.	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPH.	2,2-diphenylpicrylhydrazyl
DSC	Differential scanning calorimetry
ERK1/2.	Extracellular signal-regulated kinase protein
Etc.	Et cetera
FT-IR	Fourier transform infrared spectroscopy
GG	Garcinia glycoside
GGPP synthase	Geranylgeranyl diphosphate synthase
GI.	Gastrointestinal
GIT.	Gastrointestinal tract
GLP1	Glucagon-like peptide-1
HPMC	Hydroxypropyl methyl cellulose
hrs.	Hours
IDDM.	Insulin-deppandet diabetes mellitus
IFN-C	Interferon C
IL-B.	Interleukin B

IPP isomerase	Isopentenyl-diphosphate delta isomerase
L-carnitine	Levocarnitine
LC-MS	Liquid chromatography-mass spectrometry
MDR	Multi-drug resistance
mg/kg.	Milligram per kilogram
MIC	Minimum inhibitory concentration
mL.	Milliliter
MMT	Methylcyclopentadienyl manganese tricarbonyl
MnSOD	Manganese-dependent superoxide dismutase
NAFLD.	Non-alcoholic fatty liver disease
NAPK	Nitrogen-activated protein kinase
NPs	Nano particles
^{o}C.	Celsius
P-gp	Para-glycoprotein
PBS	Phosphate buffer saline
PEG 6000	Polyethylene glycol 6000
PEG.	Polyethylene glycol
PTX or TM	Paclitaxel
ROS	Reactive oxygen species
RPM	Revolution per minute
SA.	Sennoside type A
SB	Sennoside type B
SDS.	Solid dispersion method
SEM	Scanning electron microscopy
SEM.	Scanning electron microscope
SNC	Stabilizing nanocrystals
SOD	Superoxide dismutase
T2DM.	Type 2 diabetes mellitus

TEM	Transmission electron microscopy
TEM.	Transmission electron microscope
TGC	Triglyceride concentration
TNF-α	Tumor necrosis factor
TNF-α.	Tumor necrosis factor
TPGS	Tocopheryl polyethylene glycol succinate
UV.	Ultra Violet
W/W.	Weight per weight
XRD	X-ray diffraction

Chapter-I

Introduction

1. Introduction

1.1 Herbs in medicine

Generally, Herbs can be defined as any plant with seeds, leaves and/or flowers that is used in flavoring, food and spicing, medicine and perfume. And from botanical aspects any plant that lacks a woody stem and stays down on the ground after it bears flowers is called a herb, many people may confuse between plants and herbs, the former is a comprehensive word that can be utilized to refer to any plant in plant kingdom, however the latter is used to describe any plant that's particularly used by humans for various purpose like food, treatment. etc. To begin with glycosides are a wide group of chemical substances obtained after catalysis of secondary plant metabolites by plant enzymes namely glycosyltransferases, furthermore glycosides can undergo other reactions like oxidation, degradation and acylation these serve critical functions such as regulation of plant growth, allelopathy that is suppression of growth of other plants, aids in plant protection against herbivores and pathogens. Also, production of glycosides can be a reflex to the environmental condition, factors can broadly be classified into two, abiotic and biotic, as an instance for the former (humidity, temperature, sunlight, and the constituents of soil.) while for the latter it includes (co-existing plants and plant herbivores) *(Elvin-Lewis et al.,2001), (Pal et al., 2003).*

1.2 General definition of Glycosides

In terms of parts of glycoside, these compounds are composed of two parts namely, glycone and aglycone, the former or glycone is the sugar part that is responsible for the solubility of the glycoside as well as its PK and PD, usually being monosaccharide most common of which is glucose, others can be arabinose, xylose, rhamnose and fructose, other than monosaccharides, di-, tri-, and even tetra saccharides can be present. The second part is called aglycone or (genin) or (non-sugar) that comprises of the biological or therapeutic activity. the link that binds between these two is called the glycosidic linkage, that's not breakable by digestive enzymes, according to which glycosides can be classified to four groups: *(Bartnik, M. et al.,2017)*

- O-glycosides, that comprises of the most common type in which an oxygen is bonding between two parts.
- C-glycosides, in which a carbon atom is the linkage, this category is resistant to hydrolysis.
- N-glycosides, as the name suggests, NH group is the linkage widely present in nucleosides.

- S-glycosides such as in thioglycosides, a thiol group (SH) is linking between sugar and genin.
- Another classification can be on the basis of the chemical group of the aglycon portion, categorized into the followings: *(Soto-Blanco et al.,2022)*
- Anthraquinone
- Coumarin
- Flavonoids
- Terpenoids
- Saponin
- Phenols

1.3 Formulation of different herbs for medical purpose

Various Methods are available for extraction of such compounds from plants, including (percolation, maceration, Soxhlet extraction, pressurized liquid extraction, microwave assisted extraction, etc.,) these compounds exert various different pharmacological actions involving, anti-inflammatory, anticancer, antifungal, antibacterial, cardiotonic, antiproliferative, antiviral, etc. *(Pal et al., 2003)* .

1.3.1 History of different herbs formulation

Since the early dawn of humanity herbs have been known for their use as remedy, as per (Winslow and Kroll 1998) the very first evidence of herbal use goes back to Neanderthal period also in universal level in the declining years of 20th century herbalism has become a great concern and interest. for diverse purposes, people excel to control over their own medication or in other words to self-medicate, especially from the concept that herbal medications are safe and “never harmless” some folks assume it’s even more beneficial than chemical drugs.

So, the medicine that is based on use of natural compounds for either treatment or prophylaxis is denoted as herbal medicine.

As per WHO definition, that states it as “comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today” herbal medicine comprises for around 75-80% or even more of drugs used worldwide.as an instance in rural vicinities many factors contribute utilization of herbs as medicament, including cultural influence, environmental factors based on idea that once a disease appear in an area, nature absolutely has the cure for it, and also due to lack of chemical

or synthetic type of medicine in such areas. kamboj et al stated that, primeval evidence for herbal medicine was in Egyptian, Indian, Greek, roman, Syrian and Chinese texts that's from 5000 years ago. Around a century ago majority of the few efficacious medicament were of plant origin like, aspirin from (Salix alba), digoxin from Digitalis lanate or known as foxglove, quinine from cinchona bark and morphine from opium poppy. In the beginning of (19^{th} century) scientific approaches were improved and hence more preferred, an increase was sensed in the desire of natural health and use of herbal preparations.

Previously it was pointed out that folks preferred herbal drugs over conventional drugs most prominent reason for this was their perception that herbs are always safe and not associated with side effects or contraindications, no doubt this pattern of thinking is wrong, since chemical or conventional drugs are derived from natural sources means also the base (herbal origin) is not necessarily free from chemical groups/actions mean to say also not safe and reliable at the same level especially with some herbs that are toxic and can be fatal with low doses even like in case of digitalis (2g) of leaves can be fatal despite that its herbal, another instance is morphine or other opiates, these are narcotic and lead to addiction and very vulnerable for misuse.

Now as De Smet et al pointed out, In Germany its obligatory for herbal remedies to have special licenses to qualify them to be dispensed reliably.

Unfortunately, due to lack of such procedures and such improvement, in other countries and due to reckless use of herbal drugs Vickerw and Zollman et al reported occurrence of rapidly progressive interstitial renal fibrosis following consumption of Chinese herbs dispensed by slimming clinic, in another occasion Kew et al illustrated that Aristolochia fangchi beside resulting in kidney failure, in addition it causes cancer *(Pal et al., 2003), (Ansel's pharmaceutical dosage forms and drug delivery systems* (10th ed.).

1.4 Different techniques for Glycoside formulation

In this work, which is a systematic review of different glycoside formulations mainly from 4 kinds of glycosides namely; (Senna, Garcinia, Paclitaxel and Chrysophanol) each of which has their particular method that might resemble in some aspects, starting with senna, that exerts various desired therapeutics effect such as anti-obesity, anti-neurodegenerative, and so on, but for sure none of these effects can be achieved without an efficient formulation. two methods are revised and compared both intended for oral administration, one by wet granulation technique implementing (lactose MCC) as excipient secondly, biogenic fabrication technique

is utilized that's superior over the former, by using senna as reducing agent and silver ion will be reduced to metallic silver and used in colon cancer treatment and anthropoidal infection (*Dhoble et al., 2019), (Al-Ghamdi et al., 2020)* .

Shifting to Chrysophanol, an anthracene derivative obtained from various different organisms mean to say its source is not only confined with plants but also, fungi, bacteria and so on.

For this phytochemical two formulations were selected one being a topical hydrogel that utilized Carbopol as gelling agent, the word topical is not only restricted to the skin but also ocular, rectal even oral can be used.

Steps of formulation include six steps that will be illustrated in upcoming chapters using PEG6000 and HPMC as sole excipient. Second formulation included is Chrysophanol phospholipid complex in an attempt to increase its absorption and bioavailability by utilizing colloidal systems thus incorporating the hydrophobic drug inside hydrophobic core surrounded by hydrophilic polymer to ease solubilization thus improving absorption *(Yusuf et al.,2019).*

Now, shifting to third glycoside, Paclitaxel; it's a tricyclic diterpene mainly derived from bark of pacific yew tree, has a main therapeutic action which is exerting anticancer effect through stabilization of microtubules through inhibiting depolymerization. Both formulations are non-sized, Firstly, paclitaxel nanofiber preparation is illustrated, using Stabilizing nanocrystal method in which TPGS is the sole excipient plus functioning as P-gp inhibitor. That successfully exhibited metastasis inhibition *(Liu et al.,2010)*.

Secondly; hydrogel formulation is included that's also nano-sized however its characteristic feature is being (self-assembling) as, derivative of Taxol is used (Taxol-SA-GSSG) easing the hydrolysis process following which gel will be formed, only requiring time; as it was displayed that by decreasing time yield was increasing *(Wang et. Al., 2012).*

Fourth and last glycoside is Garcinia glycoside, extracted from fruits and plants including Gamboge and mangosteen. It exhibits various pharmacological effects, including anti-obesity, cardioprotective, hepatoprotective and mainly antioxidant mean to say anti-cancer.

Unlike previous glycosides, for garcinia 4 methods of formulation have been included and reviewed. First method comprises of topical dosage form formation by simple gel preparation method utilizing sodium carboxymethyl cellulose (CMC-Na, ethanol, methylparaben, and

100% deionized water *(Kuswahyuning et al., 2019)*. Secondly, dosage form intended to be topical, nano-sized by encapsulation and Tween 80, Span 80 were included as surfactants *(Mulia et al., 2018).* In figure (1) these phytochemicals that are explained in this study are figured.

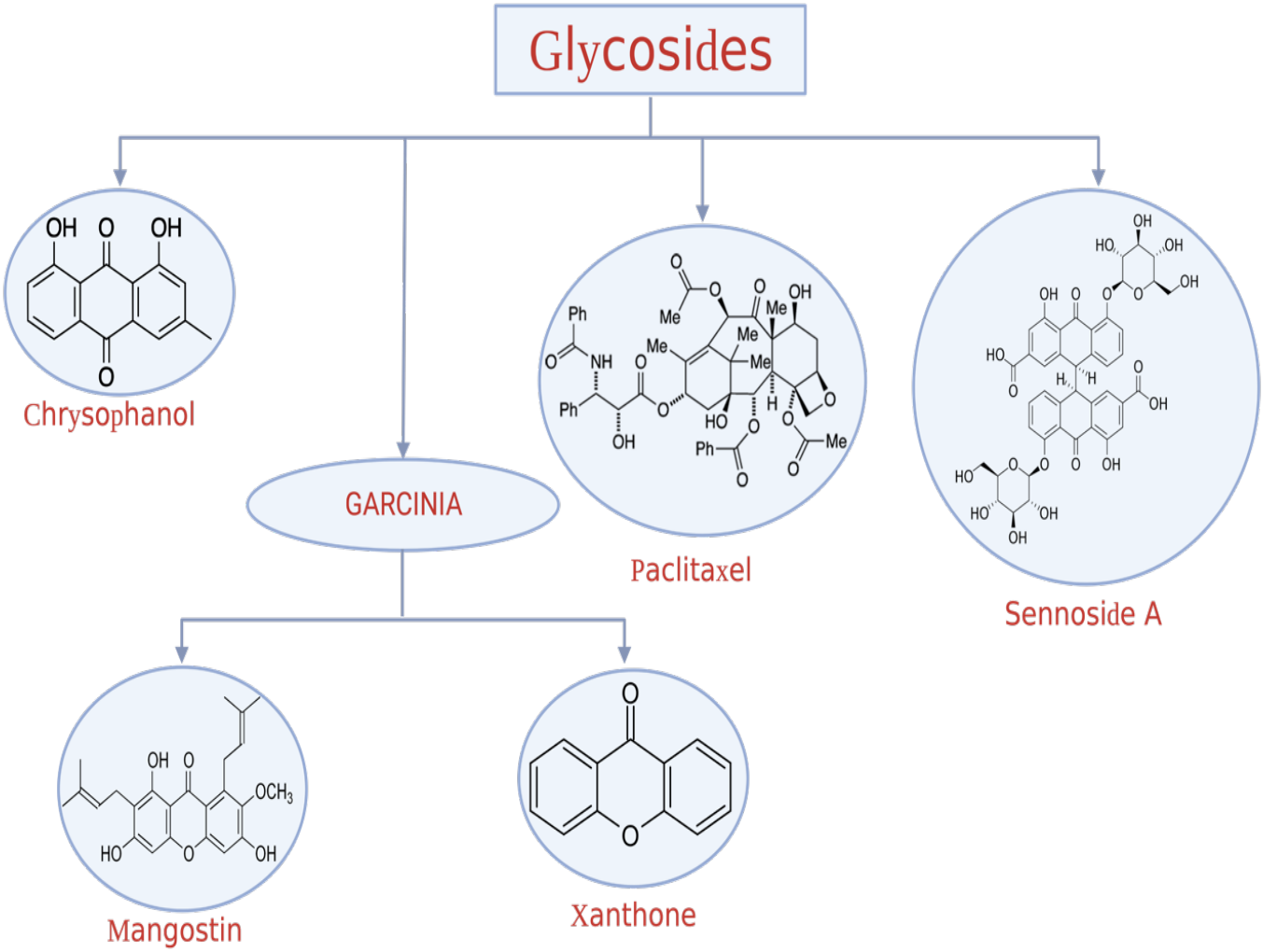

Figure 1: Types of glycosides that were explained in this study are sennosides, garcinia, paclitaxel, and chrysophanol.

Chapter-II

Scope and aim of the study

2.1 Problem Statement

As a definition of pharmacy, it's the science and art of discovering, producing, preparing, dispensing, reviewing, and monitoring medications aiming to ensure the safe, effective, and affordable use of medicines.

And a drug is illustrated as a substance or more accurately a formulation designed to be utilized in the diagnosis, mitigation, treatment, and prophylaxis of diseases and disorders, for the drug to exert its action (s) and to result in desired mentioned consequences, It should be successfully prepared in a suitable unique dosage form with the specific quantity that's determined by the route through which it'll be administered plus its own physicochemical and pharmacological characteristics for sure. As is customary four main disciplines are there in pharmacy namely (pharmacology, pharmaceutical chemistry, pharmaceutics, and pharmacognosy).

Assuredly binding between these aspects is of essential importance for the improvement of the pharmacy field in our graduation thesis under the title (Novel formulation approaches for glycosides) our main concern is combining pharmacognosy and pharmaceutics the latter is concerned with the development of new effective dosage forms in terms of safety, long shelf life, half-life, increasing solubility, and bioavailability…etc.

Pharmacognosy is an applied science concerned in acquiring knowledge of all aspects of crude drugs and other natural substances of pharmaceutical importance by the application of various scientific disciplines. The purpose of this study is first to exhibit specific glycosides and their characteristics, pharmacological action, current formulation if available, and if not available why it's not available. find out the best way for the formulation of specific drugs of our concern, by first determining defects and limitations in the currently available version of them, and answering the question of why this has occurred.

And how can we solve that particular issue?

The types of glycosides we have discussed have a wide range of pharmacological effects, however, these effects cannot be attained without formulation. The sorts of the target organs, as well as the types and natures of the plants or medications, influence the formulations as well. *(Ansel's pharmaceutical dosage forms and drug delivery systems*, 10th edition)

2.2 Aim of the study

- Demonstrating different techniques to formulate Garcinia glycoside orally, and topically.
- Differentiation between these different techniques for Garcinia formulation orally, and topically.
- Different techniques to formulate Sennoside orally.
- Differentiation between those two techniques used for Sennosides orally.
- Explaining and showing Different techniques to formulate Chrysophanol.
- Introducing the most effective method to formulate paclitaxel.
- Showing different types of anticancer from natural sources or glycosides.

2.3 Objectives

- Reviewing, summarizing, and comparing many preparation methods for Garcinia glycosides that are mostly for treatment and prevention various types of disease mainly cancer.
- Reviewing, epitomizing, and comparing the best methods for formulation sennosides as determined by various investigations, and differentiation between classic technique and advance technique to formulate sennoside glycosides.
- Examining and looking for appropriate formulation methods for paclitaxel and Chrysophanol, and searching for the safest technique to formulate sennoside from senna leaves.

Chapter-III

Literature review

3.1 Garcinia Glycoside

The Gamboge plant contains a natural chemical known as garcinia glycoside. largely used as an anti-cancer medication by a variety of mechanisms such as cell apoptosis, topoisomerase activity, inversion of multidrug resistance, and others (*Fu et al., 2013)*. Several animal studies show that pure Garcinia Glycoside has a half-life of 2.2 hours when given orally, and it can't give and use topically without formulation. Unformulated Garcinia Glycoside has a high metabolic rate, produces toxicity, and is inefficient as a medication (*Li WJ et al., 2013), (Fu et al., 2013).*

3.1.1 Properties of Garcinia glycoside

Garcinia Glycoside has a short half-life, which isn't sufficient for therapeutic purposes. It has low solubility in aqueous solutions but a high solubility in organic solvents.

3.1.2 Pharmacological activities of Garcinia Glycoside

Figure 2 outlines the pharmacological effects of this plant component (Hur et al., 2014), (Apovian and C.M, 2016), (*Panda et al., 2012), (Barve and K., 2019).*

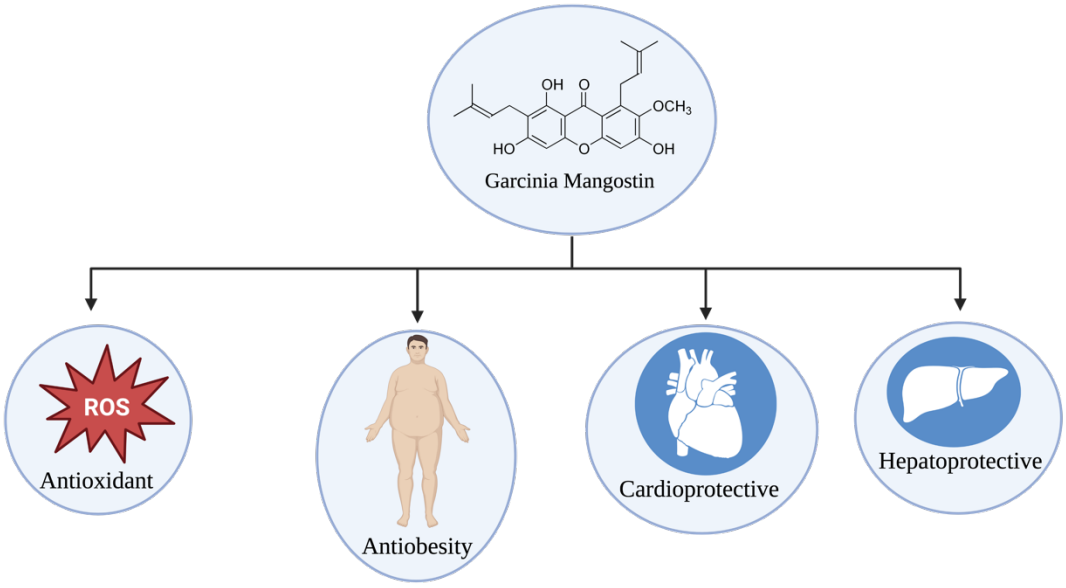

Figure 2: Pharmacological activities of Garcinia glycosides.

3.1.2.1 Antioxidant effect

Excess oxidants and the production of free radicals can cause oxidative damage. Factors that damage macromolecules such as DNA, proteins, and lipids raise the risk of cancer. Garcinia Glycoside, which is produced from many plants, can work as an antioxidant by decreasing oxidative stress in a variety of ways *(Hur et al., 2014).*

3.1.2.2 Anti-obesity effects

Being overweight and obese are risk factors for a variety of diseases and comorbidities, including cancer, CVS diseases, and IDDM. The anti-obesity properties of GG from Garcinia indica were revealed by effects on 3T3-L1 adipocytes, reduction of adipogenesis, and enhancement of beta-oxidation *(Apovian and C.M, 2016).*

3.1.2.3 Hepatoprotective activates

Garcinia Indica aqueous extract at 400 or 800 mg/kg can decrease AST levels, which in turn diminish AST enzyme activity, resulting in the elimination of liver injury. The Garcinia Indica has another way of protecting hepatic cells from toxins, similar to the Silymarin process *(Panda et al., 2012).*

3.1.2.4 Cardioprotective activities

According to various studies on mice, aqueous extracts of Garcinia Indica can modify myocadiac cells before cell damage by lowering TGC levels and total cholesterol, but they cannot protect the heart against myocardial damage or necrosis *(Barve and K., 2019).*

3.1.3 Different methods of Garcinia formulation

The drug release pattern is an important factor of bioavailability for oral medications with poor gastrointestinal solubility and high permeability. According to several investigations on the substance's composition, there are numerous ways to develop oral and topically applied dosage forms from Garcinia Glycoside extract *(Liu C, 2008).* The most promising methods are nano-emulsion and simple gel preparations that are commonly used to generate topical dosage forms from GG. This article will review and differentiate the various techniques for developing

pharmacological dosage forms from GG. Figure 3 depicts several approaches to the formulation of Garcinia glycoside.

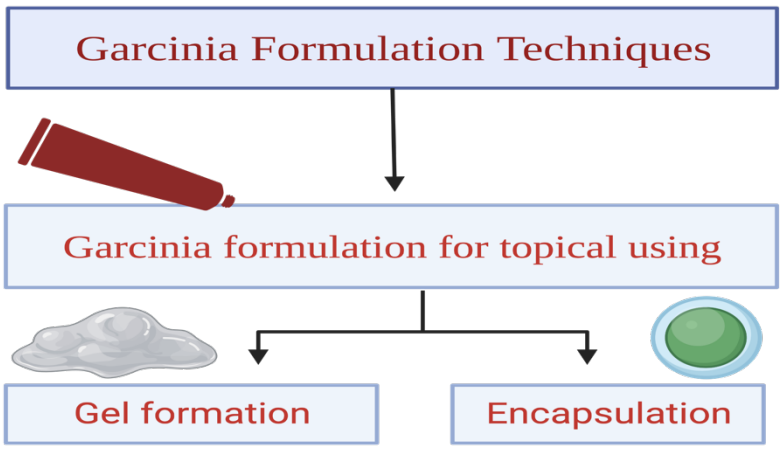

Figure 3: Garcinia glycoside can formulate as formulation by gel formulation, and encapsulation.

3.1.3.1 Preparation of gel formulation from Garcinia according to (Kuswahyuning' study)

Garcinia glycoside has antioxidant characteristics that may be utilized to treat skin conditions caused by oxidative stress. The pericarp extract from Garcinia Mongostana fruit is prepared as a gel dosage form with the capacity to release and support skin delivery (Kuswahyuning et al., 2020). As previously noted, the antioxidant activity of the fruit pericarp extract of Garcinia mangostana L. is determined by utilizing the radical scavenger 2,2-diphenyl 1-1-picrylhydrazyl (DPPH) technique *(Kuswahyuning et al., 2019).*

3.1.3.2 Gel formulation

The gel basis is composed of 2% of sodium carboxymethyl cellulose (CMC-Na), 10% of ethanol, 0.1% of methylparaben, and 100% deionized water (deionized water is one of the kinds of water that through a series of the chemical process, all the dissolved mineral particles or ions are removed from it) *(Kuswahyuning et al., 2019).*

Deionized water is mixed with CMC-Na, which is then hydrated overnight with 750 rpm agitation. Then methylparaben is added. The APA, which is a 20% Garcinia mangostana L. fruit pericarp extract, is added to the gel base that was previously prepared with homogeneous and continuous agitation or stirring to achieve a uniform gel formulation. The APA is

prepared by dissolving 20% of the drug powder extract in deionized water *(Kuswahyuning et al., 2020)*. Figure 4 shows the steps of gel formulation.

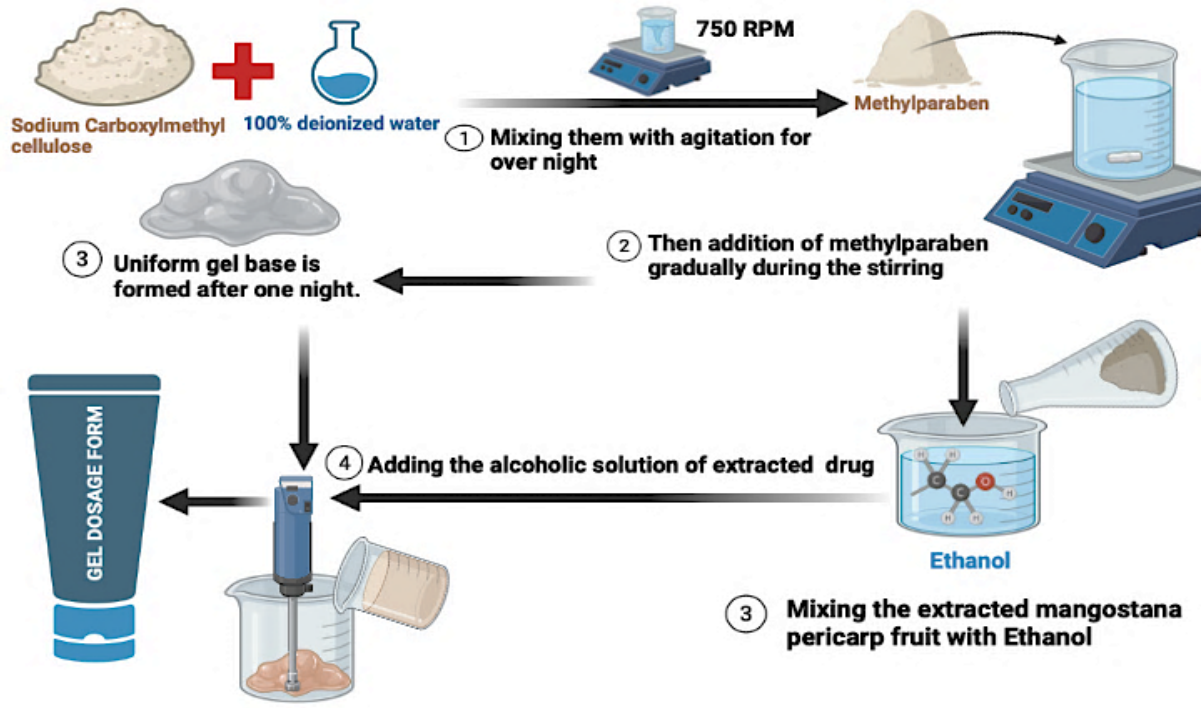

Figure 4: The steps of the gel formulation technique.

3.1.4 Preparation of topical dosage form by encapsulation of Garcinia Glycoside (according to Kamarza Mulia' study)

Another topical formulation of Garcinia glycosides extract is generated by entrapping Garcinia Mangosteen in a virgin coconut oil-based nano emulsion. A high-speed homogenization technique is used to prepare virgin coconut oil nano emulsion as the oil phase of the encapsulating system. Tween 80 and Span 80 are also combined as oil-in-water surfactants, with distilled water serving as the aqueous phase. This encapsulation approach delivers garcinia topically through the skin. Finally, this combination can be used topically to treat bacteria, fungi, and viruses (especially for fungal infections of feet) *(Mulia et al., 2018)*.

3.1.4.1 Extraction of mangosteen

The powdered mangosteen fruit rind is macerated in ethanol for a week to extract the glycosides (Pedraza et al., 2008). The dry powder must be separated after extraction by using an equal

volume of ethyl acetate and water. Then Rota evaporator is used to dry the mangosteen-rich ethyl acetate portion to generate dry mangosteen extract powder. A UV spectrometer with a wavelength of 316 nm is used to determine or measure mangosteen in the extract *(Jaiswal et al., 2015), (Mulia et al., 2018).*

3.1.4.2 Nano-emulsion preparation

Oil phase ingredients include virgin coconut oil, mangosteen extract, and the surfactants Tween 80 and Span 80. In order to achieve a hydrophilic and lipophilic balance in the formulation, a combination of surfactants is required. Mangosteen extract is mixed in virgin coconut oil in a ratio of 1:2.2 (mg per mL), and a homogenous solution is formed by stirring at 750 rpm. (Communique, 2017) The oil phase is prepared by mixing virgin coconut oil and mangosteen extract with Tween 80 and Span 80 under stirring at 500 rpm for 10 min. The nano-emulsions are formed by mixing the oil phase with distilled water by the ratio of 1:1.04 (v per v) and stirring at 750 rpm until they will be mixed well. To homogenize coarse emulsion the high-speed homogenizer, Ultra Turrax, T18 is used for 15 minutes under 6000, 8000, and 10000 rpm *(Lerche et l., 2011), (Mulia et al., 2018).* Nano-emulsion steps are illustrated in figure 5.

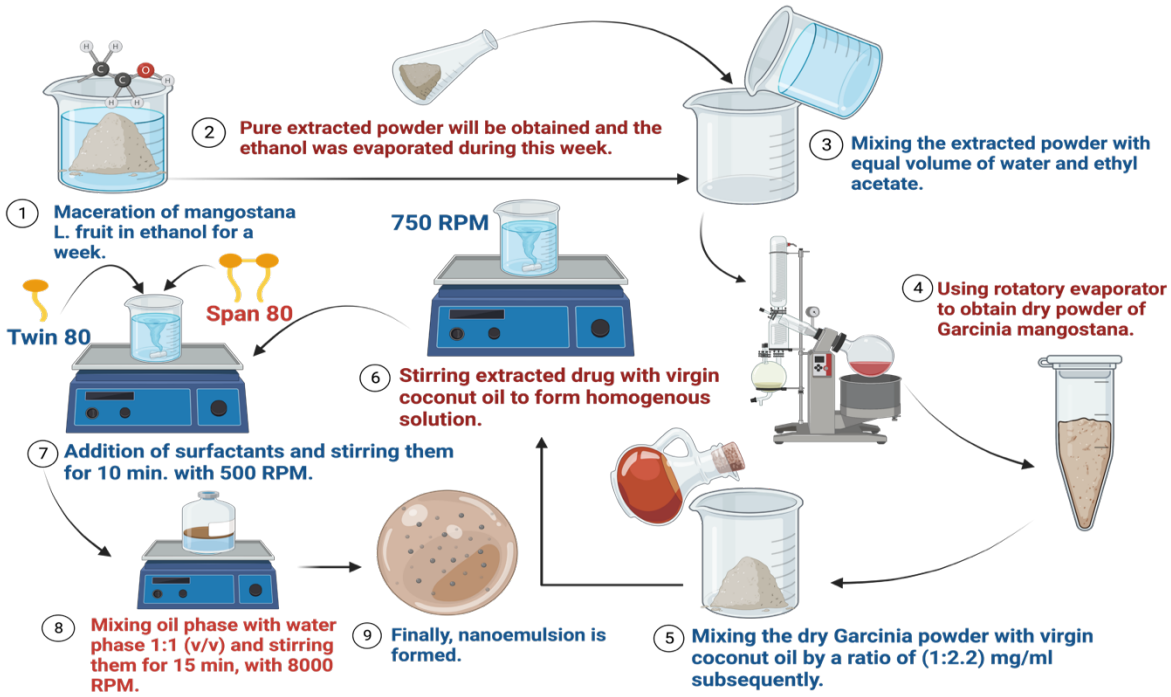

Figure 5: The steps of nano-emulsion preparation.

3.2 Sennoside (A) and Sennoside (B) Glycoside

Senna is also referred to as senna leaves, senna folium, cassia senna, senai kipatti, sonamukhi, and mobay senna. Senna is a plant with leaves made up of Cassia Angustifolia, belongs to the Leguminosae family. (Khandelwal) Senna leaves have different names in different regions and nations; for example, Tinevelly Senna is the name given to senna leaves in India (*Rangari, 2012).* The two primary anthraquinone glycosides found in senna leaves are sennoside A and sennoside B. These two kinds of glycosides are isolated from senna leaves. Additionally, senna leaves contain minor amounts of the sennosides C and D *(Dhoble et al., 2019).*

3.2.1 Solubility and properties of sennoside A and sennoside B Glycoside

Sennosides are almost completely soluble in organic solvents like ethanol and methanol and very little soluble in aqueous solutions *(Rangari, 2012).*

3.2.2 Pharmacological activities of sennoside A and sennoside B Glycoside

Senna has various pharmacological properties, including anti-obesity, hypoglycemia effect, hepatoprotective action, and anti-neurodegenerative impact. Senna's primary pharmacological activity and the most well-known one is using it to treat chronic constipation. The pharmacological actions of SA and SB are displayed in both Table 1 and Figure 6

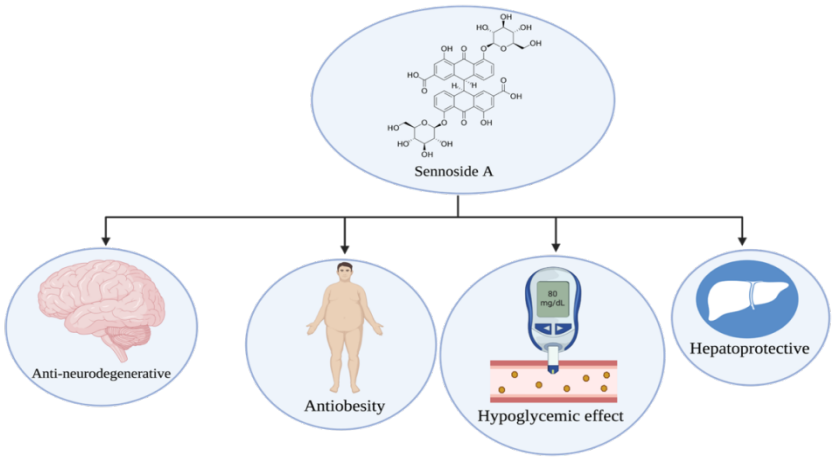

Figure 6: Different pharmacological activities of sennosides. *(Dhoble et al., 2019)*

Table 1: Shown the pharmacological activities of SA and SB *(Dhoble et al., 2019).*

Pharmacological activities	Pattern of action
Anti-obesity	More restoration of GLP1 in post prandial
Hypoglycemic effect	Inhibition of alpha glucoamylase, inhibition of ERK1/2
Hepatoprotective effect	Inhibition of hepatic stellate cells mutation and proliferation
Anti-neurodegenerative effect	Stabilizing of human lysozyme

3.2.2.1 Anti-obesity effect

Due of the lack of exercise and high-calorie intake, obesity is a serious health problem. The most recent studies have demonstrated that ingesting sennoside pills at doses of 30 mg/kg can increase postprandial GLP1 restoration, which is accompanied by a reduction in body weight *(Dhoble et al., 2019).*

3.2.2.2 Hypoglycemic effect

Together, Chrysophanol and Sennoside are known to treat T2DM via the following mechanisms: inhibition of alpha glucoamylase and blockage of ERK1/2, which is the primary pathway to lower GLP1. Sennoside tablets, when taken in doses of 30 to 50 mg/kg, boost the body's peripheral tissues' sensitivity to insulin *(Dhoble et al., 2019).*

3.2.2.3 Hepatoprotective effect

As a result of excessive hepatic lipid buildup, nonalcoholic steatohepatitis, liver cirrhosis, and ultimately hepatocellular carcinoma, non-alcoholic fatty liver disease NAFLD are linked. By defending the mitochondria, sennosides prevent hepatic steatosis. Additionally, they achieve hepatic cell protection against fibrosis while simultaneously inhibiting hepatic stellate cell mutation and proliferation *(Dhoble et al., 2019).*

3.2.2.4 Anti-neurodegenerative effect

In older or aging humans, particularly in men, amyloid-like clumps from misfolded proteins can frequently lead to neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and Creutzfeldt-Jakob disease. The main treatment for many

neurodegenerative illnesses are the inhibition of amyloid fibrillation. Additionally, 20 micrograms of sennoside per 1 ml of solution inhibit amyloid fibrillation which is resulted in protecting humans against neurodegenerative diseases *(Dhoble et al., 2019).*

3.2.3 Sennosides formulation

Patients are at risk for several side effects and toxicities when unformulated sennosides are administered, and none of the pharmacological activities mentioned occur *(Al-Ghamdi et al., 2020).* The formulation is necessary to achieve the most effective pharmacological actions and to cover up Sennosides' adverse effects, which include primarily colon cancer, skin rash, nausea, and vomiting. According to different studies and researches on sennoside formulations, there are many methods for preparing and formulating sennoside tablets but the most popular one is the production of sennoside tablets via the wet granulation technique *(Kalia, 2011).* Another advanced method for preparing sennoside tablets that are consumed to treat the digestive disorder and anthropoids' infection in the colon by microbes is Biogenic fabrication to produce nanoparticles of SA *(Al-Ghamdi et al., 2020)* .Figure 7 is shown different techniques for sennoside A formulation.

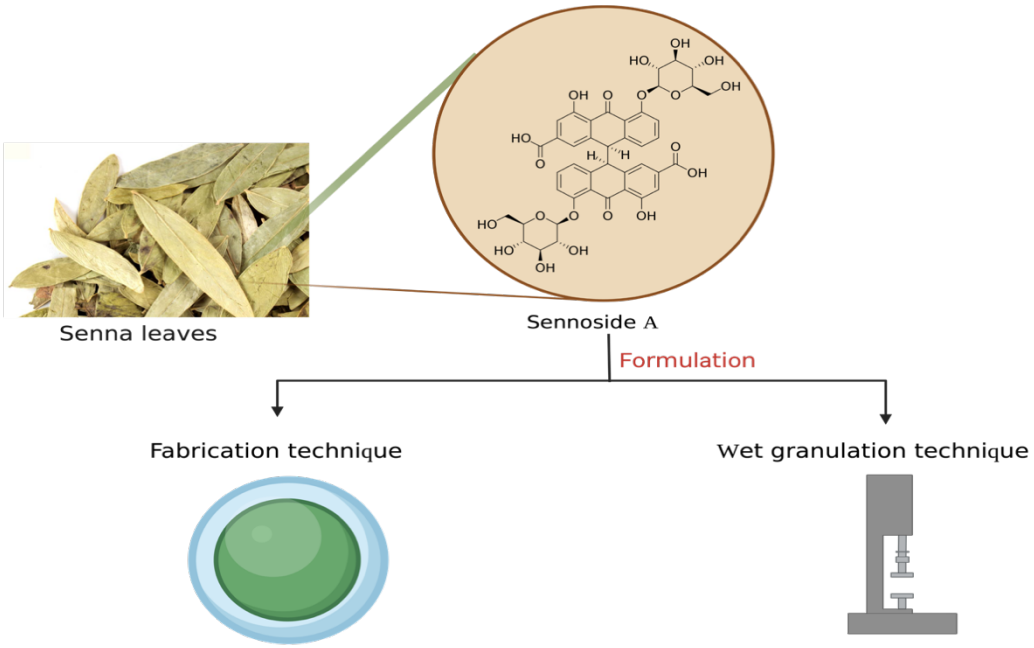

Figure 7: Shows different techniques for Sennoside A formulation.

3.2.3.1 Preparation of Sennoside A and B tablets by wet granulation method (according to Leena Raju DHOBLI, 2019' study)

Sennosides are extracted from senna leaves via a variety of processes, and the extract is then formulated by wet granulation. Wet granulation is used for a variety of purposes, including enhancing powder flow properties, dose uniformity, product bulk density, volumetric dispensing, managing the rate of medication release, lowering dust production, lowering employee product exposure, and enhancing product appearance *(Rajesh Agrawal et al., 2011)*. Wet granulation techniques transform small or big medication powder particles into physically larger and stronger agglomerates with the enhanced flow, compression, and uniformity properties *(Yamasaki et al., 2009)*. Fundamentally, the wet agglomeration properties of powders are governed by three properties: Wetting and nucleation come first. Consolidation and growth come next, followed by breakage or attrition *(Sakr et al., 2012)*. Like all processes, this one has several advantages and disadvantages, which are listed in Table 2.

Table 2: Advantages and disadvantages of conventional wet granulation techniques *(Rajesh Agrawal et al., 2011)*.

Merits	Demerits
Improving flow properties and compression characteristics, and increasing density of powder.	The process is costly due to labor, space, time special equipment, and energy requirement.
Better distribution of soluble drugs and color if added in binding solution	Multiple process and complex
Reduction of dust hazards.	Wasting of materials during the process.
Prevention from segregation of powders.	Don't be used for moist sensitive and thermo liable drugs.
Conversion of hydrophobic surface to more hydrophilic.	Aggravation is any incompatibility between the formulation components during the process.

Sennosides are extracted from senna leaves by using a variety of techniques before being formulated by using the wet tablet granulation method. Lactose-MCC complex (1:1) is used as the excipient by an amount of 138 mg of lactose-MCC complex to 1 tablet 3 in the wet granulation process, which is employed to formulate the sennoside glycoside, Furthermore, the

excipient-containing tablet is dissolved in the n-propranolol solvent system. Lubrication is also included in this procedure *(Rajesh Agrawal et al., 2011).*

To create a cohesive mass of powder, this mixture of excipients, active pharmaceutical ingredients, and solvent must first be blended. Next, the mixture must be sieved or screened eight to ten times. Finally, the wet granules must be dried at 60°C in a heat-air oven. After drying and 20 times repetitions of sieving to get homogeneous granules, dried granules are formed. After adding the lubricant or disintegrant, the ingredients must again be blended. Wet homogenous granules are the end result, and they are prepared for tablet production. The table below illustrates the steps of wet granulation *(Dhoble et al., 2019).* The steps of the wet granulation technique are illustrated in figure 8.

Table 3: Wet granulation steps for sennoside tablet preparation (*Dhoble et al., 2019).*

Name of the steps	Materials and their functions
Mixing	Mixing of lactose-MCC, Senna extract, n-propranolol. In the result coherent mass of granules is formed.
Screening	Screening or sieving of the produced mass of granules by special sieve 8 to 10 times, in order to obtain uniform mass of granules.
Drying	Drying the sieved granules at 60ºC by hot air oven.
Dry screening	Again, sieving or screening the dry granules 20 times.
Addition of lubricant	Lubricant is disintegration agent in order to disintegration of the tablet when contact with medium of fluid. And uniform of flow in the bunch and die.
Mixing	Again, mixing the dry granules and the lubricant by blender.
Tablet preparation	Tablet preparation is obtained by special instrument, for instance bunch and die.

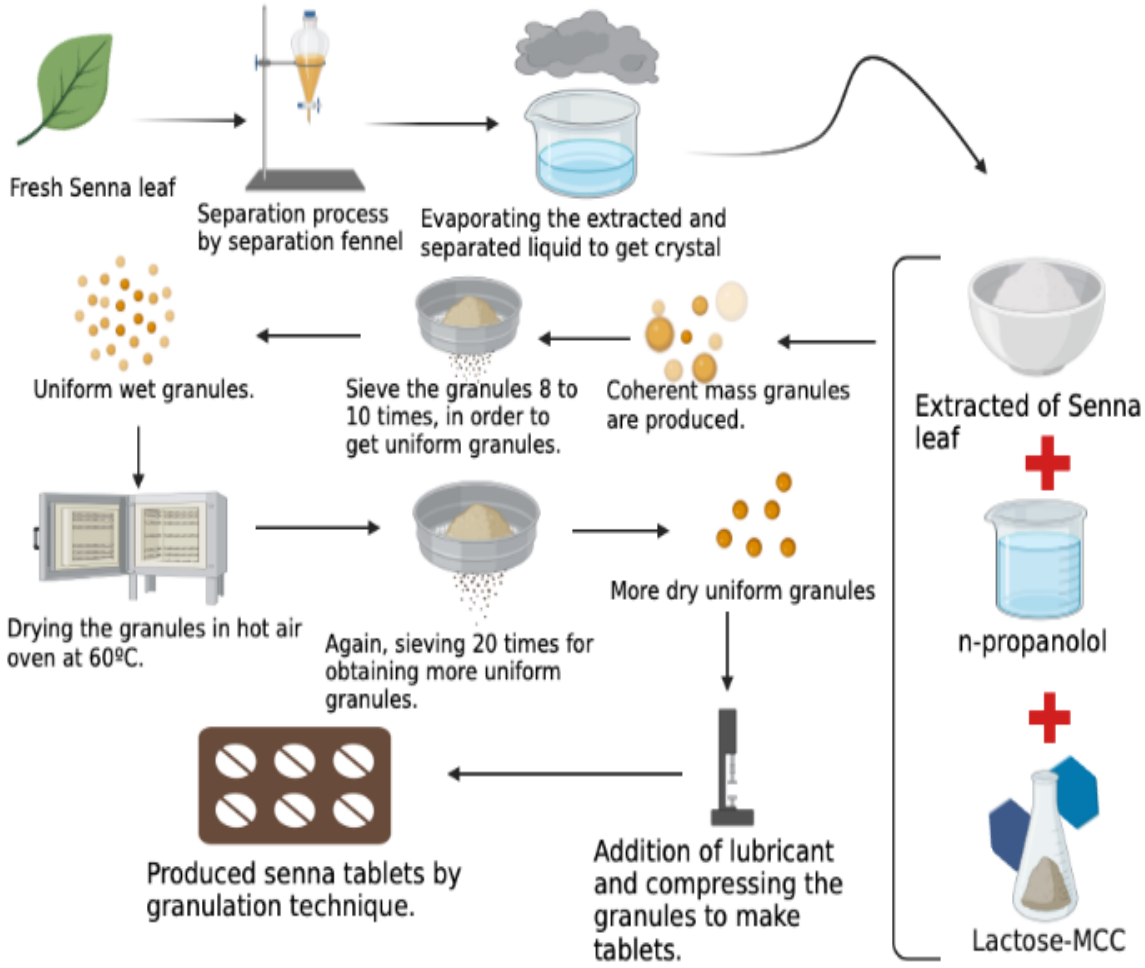

Figure 8: The steps of wet tablet granulation.

3.2.3.2 Preparing oral formulation of Sennosides by biogenic fabrication technique (according to Zoya Zaheer' study)

Ag/Sennoside nanoparticles are used in the preparation process to produce an oral formulation that can cure gastrointestinal problems and anthropoid infections in the colon. DPPH, two bacterial strains (Staphylococcus aureus and Escherichia coli), and two yeast strains (Candida albicans ATCC 1031 and Candida parasitosis ATCC 22019) are used to evaluate the antioxidant and antibacterial characteristics of Ag/SA nanoparticles *(Ledwani et al., 2012).*

The oral formulation of nanoparticle of Ag/SA is ingested, and SA is hydrolyzed in the GIT to yield Rhein -9- anthrone which is also known as (4,5-dihydroxy-10-oxo-9H-anthracene-2-carboxylate), that has antibacterial properties *(Sun and Su, 2002)* .

If SA is employed as a reducing or capping agent in the biogenic manufacturing process, a *sophisticated technology* caps silver nanoparticles, and this process is done at room

temperature. Additionally, this formulation pattern improves SA glycoside absorption. In this formulation procedure, CTAB is employed as a stabilizer to examine how cationic micelles affect fungus growth and antifungal activity *(Al-Ghamdi et al., 2020).*

Through this procedure, oral formulations for the treatment of colon infections from anthropoids are created. There are two procedures for obtaining this oral formulation. Sennoside A is extracted in the first step, and then Ag-sennoside A nanoparticles are made in the second *(Ledwani et al., 2012).*

3.2.3.2.1 Extraction of Sennoside A from fresh leaves of Senna which is *Cassia angustifolia* DEL.

Senna also called Cassia Angustifolia, is collected as its fresh leaves, which are then washed twice—once with tap water and once twice with double distilled water—to eliminate dust and other foreign substances *(Al-Ghamdi et al., 2020).*

The leaves dried by assisting the sunlight. 10 grams of the dried leaves are then added to a stoppered conical flask containing 200 mL of double-distilled water, and the mixture is heated at 80ºC for 30 minutes while being constantly stirred and heated in a water bath. After being heated in the water bath, the filtrate must cool at room temperature before beginning to be filtered by using *Whatman filter paper* to remove the waste from the leaves. As a result, the dark yellow chemical precipitate is obtained, and fresh extract must be treated by using a rotatory evaporator under a vacuum at 80°C temperature.

Sennoside A and B, aloe emodin, and Rhein glycoside are all components of the senna leaf extract *(Sun and Su, 2002).* Finally, using particular purification procedures, sennoside A is separated from the resultant dark yellow substance.

3.2.3.2.2 Fabrication of Ag/sennoside A nanoparticle

In a special experiment, sennoside A, which was previously isolated, is introduced to a conical flask containing 5 mL of an aqueous solution of AgNO3 (0.01 mole/L) and (1.4x10-4 moles) of sennoside A. sennoside A and AgNO3 must be combined, and the mixture must then be continuously stirred by a magnetic stirrer at 1500 rpm for 30 minutes. When the mixture's color changes from yellow or orange to dark brown, this indicates that the (Ag+) ions have been reduced into metallic silver (Agº). To produce silver nanoparticles, the resulting dark brown color mixture was centrifuged at 15000 rpm for a half-hour at 25 ºC. After being created, the silver nanoparticles must be dried at 80 °C and then stored at room temperature in a dark environment. To achieve the best delivery method to the colon or to treat digestive issues and anthropoid infections in the colon, the generated silver nanoparticles are loaded with sennoside A by centrifugation *(Al-Ghamdi et al., 2020)*. The steps of this method are illustrated in figure9.

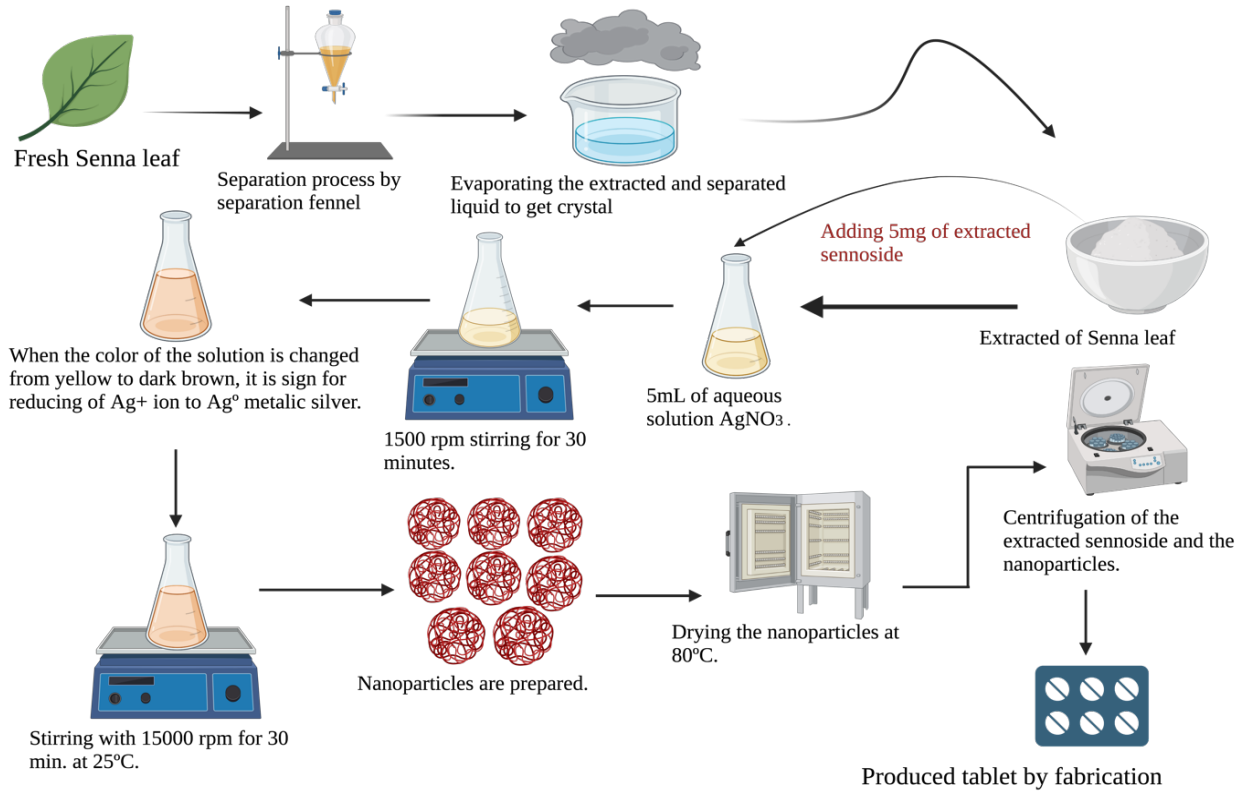

Figure 9: The steps of the fabrication technique.

3.3 Chrysophanol

It's a particular anthracene derivative that possesses a wide array of therapeutic capacities besides ecological significance and can be obtained from various natural sources including 14 genera of different families with roughly 95 or more species of plants, besides that other organisms like bacteria and fungi can contain Chrysophanol. in term of plants it found in rhizomes, leaves, roots, pods, flowers, and bark for the first time it was detected in (rheum rhubarb) that belong to Polygonaceous family *(Yusuf et al., 2019).* Source of Chrysophanol from plant kingdom is illustrated in table 4.

Table 4: Sources of Chrysophanol from the plant kingdom *(Yusuf et al., 2019).*

Family	Genus	Species	Part of plant
Polygonaceae	remex	*R. acetosa* *R.dentatus*	roots
Fabaceae	senna	*S. italica* *S. macranthera*	Pods, bark
Asphodelaceae	Aloe	*A. vera* *A. ferox*	Leaves

In insects also Chrysophanol can be detected which are show in table 5, even though not very common however sometimes released for defensive purposes *(Yusuf et al., 2019).*

Table 5: Sources of Chrysophanol from insect**:** *(Yusuf et al., 2019).*

Family	Genus	Species	Part
Adelgidae	Adelges	*A. tsugae*	Eggs, adults
Chrysomeldae	Galeruca, trihabda	*G. tanaceti, T. geminata*	Eggs, Larvae

The third organism in which Chrysophanol is present in fungi and the first time was (Penicillium *islandicum*), many times observed with endosymbiotic fungi mean to say fungi that is living in the body of other organisms like marine organisms and even plants *(Yusuf et al., 2019).* Chrysophanol sources from fungi are shown in table 6.

Table 6: Chrysophanol sources from fungi *(Yusuf et al., 2019).*

Family	Genus	Species	Place or part
Trichocomaceae	Pencillium	*P. oxalicum*	Curcuma wenyujin
Pleosorbaceae	Phaeospheria	*P. spartinae*	Sea foames
Parmeliaceae	Asahenia	*A. chrysantha*	Whole thallus

3.3.1 General properties of Chrysophanol

Characterized by diverse actions on biological system that qualifies it to be utilized as an Anticancer; hepatoprotective; neuroprotective; anti-inflammatory; antimicrobial; antiplatelet& Anticoagulant; Antiproliferative; antiulcer *(Yusuf et al., 2019).*

It's also good to mention that Chrysophanol is an essential constituent in many of the (TCM and TKM) namely, traditional Chinese medicine and traditional Korean medicine respectively, and had used in: (blood stasis syndrome, chronic kidney disease, constipation, obesity, inflammation, and hypotension…etc.) *(Yusuf et al., 2019).*

basically, it's an anthraquinone derivative that is composed of three rings (tricyclic) out of which two of them are aromatic. Anthraquinones are secondary metabolites used as a coloring agent, in the food industry and textile industries. As a precursor to derive various anthraquinones 9,10-anthracene-dione is used, to which methyl, methoxy, hydroxyl, and carboxyl groups are added so Chrysophanol is apparently a derivative of this compound by addition of two hydroxyls and one methyl group to become (1,8-dihydroxy-3-methyl anthraquinone) also termed as Chrysophanol acid *(Yusuf et al., 2019).*

Keeping in mind that glycoside is a glucoside that is a sugar derived from glycoside. In the former, the substance yields sugar on hydrolysis while in the latter it has a functional group attached to a sugar, (glycone and aglycone part). Other chemical properties include:

- Formula : $C_{15}H_{10}O_4$ *(PubChem, 2004)*
- Molecular weight: 254.24 D*(PubChem, 2004)*
- H bond donor count: 2(PubChem, 2004)
- H bond acceptor count: 4 *(PubChem, 2004)*
- Melting point: 196 °C *(PubChem, 2004)*

It's a crystalline powder that appears dark yellow to brown in color, in terms of solubility it has low aqueous solubility and its solution shows a red color after adding alkali or concentrated sulfuric acid to it, however, originally it was yellow in color *(PubChem, 2004).*

3.3.2 Pharmacological activity of Chrysophanol

The important pharmacological activities of Chrysophanol are shown in figure 10.

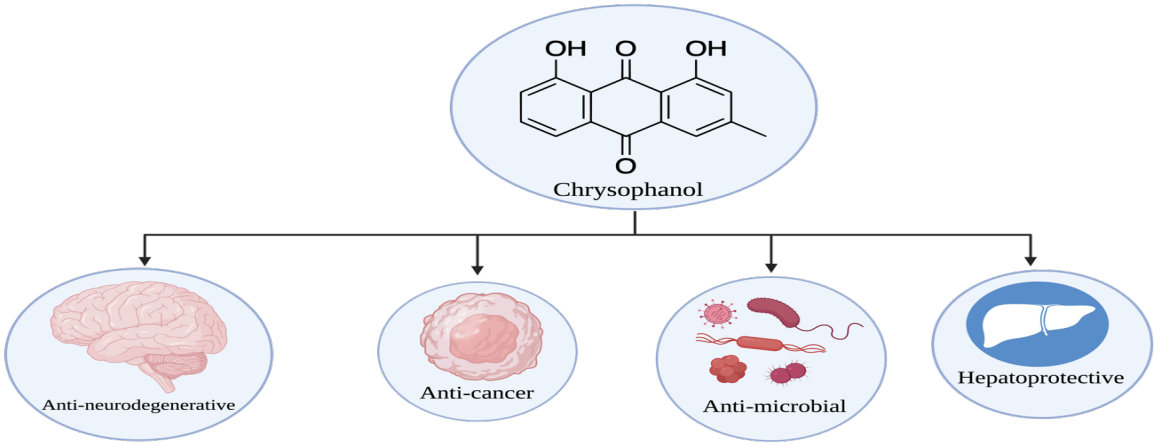

Figure 10: Shows different pharmacological activities of Chrysophanol *(Yusuf et al., 2019), (Zhang et al., 2014).*

3.3.2.1 Neuroprotective activity

The region in the brain responsible for memory either long or short term is the hippocampus which is affected in Alzheimer's disease (AD) Chrysophanol also decreases injury or harm in the such area by its antioxidant effect *(Yusuf et al., 2019), (Zhang et al., 2014).*

In an overlap of actions, neuroprotection is achieved through antioxidant and anti-inflammatory action, the latter also shows a protective effect on cerebral ischemia-reperfusion *(Xie et al., 2019).*

3.3.2.2 Hepatoprotective activity

Chrysophanol can preserve hepatic tissue from injury through its anti-neoplastic activity. (HePG2/CYP2E1) cells were treated with ethanol at a concentration of (100µm) was effective in decreasing GGT (gamma-glutamyl transpeptidase) activity the latter is required for GSH homeostasis *(Yusuf et al., 2019), (Qian et al., 2011).*

Also, in mice with (LPS/D-GAIN) induced acute hepatic injury (TNF-α and IL-6) were reversely regulated by the action of Chrysophanol *(Yusuf et al., 2019).*

3.3.2.3 Antivirus and antibacterial activity

A study was conducted on JEV infection which is a viral infection, Chrysophanol was capable of demolishing the viral envelope and has activated gas-driven genes as indirect action of IFN-C triggering host innate immune response, even though the exact mechanism through which Chrysophanol imparts antibacterial action is not known however it was found that it can inhibit the formation of biofilm in E.coliATCC25922 and the MIC values for colon bacillus and Neisseria gonorrhea were 3.13 µg/ml and >75µg/ml respectively *(Xie et al., 2019), (Qian et al., 2011).*

3.3.2.4 Anticancer effect

By two major mechanisms, Chrysophanol will induce its anticancer effect, either by inducing apoptosis or by antiproliferative activity. Regarding the former, it was observed that exposure of HL-7702 cells to Chrysophanol with concentration from 0-100µm showed no evidence of cytotoxicity besides that in other cells like (HePG2, HCT8, A549, SGC7901, and MDAMB-231) again signs of cytotoxicity were absent however further research revealed how Chrysophanol inhibited further growth of cancer cells. at the concentration (10,50,100µg/ml) it has little effect on breast cancer cell lines (MCF-7, T47D) as well as colon cancer cell lines (HCT-116) *(Xie et al., 2019)*. And through antiproliferative action, it exerted an effect on breast cancer (MCF-7), gastric cancer (7901 cells) melanoma (A375 cells) and also it was detected that Chrysophanol arrested cell cycle progression of (HeP3B hepatoma cells) in the S phase and through (ROS) production, (MAPK) activation, and mitochondrial (Ca) overload Chrysophanol inhibited the cell viability as well as invasiveness of (ES2) and (OVCAR3 cells). Chrysophanol inhibited phosphorylation of (NF-κB/cyclin D1 and NF-κB/BCl2) pathway that resulted in the inhibition of breast cancer cell cycle progression and proliferation *(Xie et al., 2019).*

3.3.3 Chrysophanol formulation

Different techniques to formulate Chrysophanol are shown in figure 11.

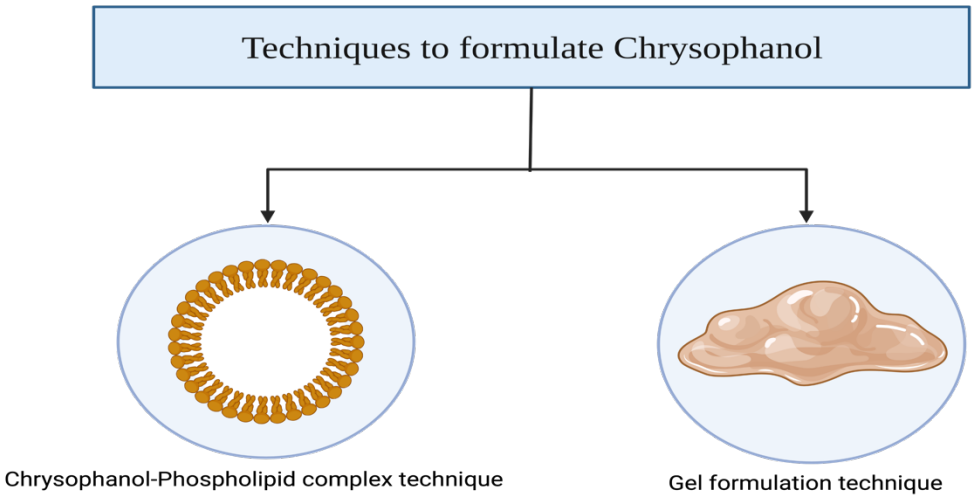

Figure 11: Different techniques to formulate Chrysophanol are the gel formulation technique and the Chrysophanol-phospholipid complex technique.

3.3.3.1 Chrysophanol novel formulations (formulation and in-vitro evaluation of Chrysophanol topical gel) according to (Vasudevan et al., 2011) study

In a study aiming at the use of a suitable concentration of Carbopol and a suitable concentration of different permeation enhancers to formulate a topical gel of Chrysophanol to control or prevent infections as these are the major problem in wound management besides that gels and/or hydrogels are considered as valid nominates for oral, rectal, ocular cutaneous as well as subcutaneous routes to be administered as it has many merits over other routes like it's easy and convenient to use, high residence time on the skin, not greasy.. etc. Carbopol is considered as a gelling agent in this study, its viscosity depends on pH however the factor that influences the release of the drug from the preparation is the properties of the vehicle as well as the drug either chemical or physical. The procedure by which the gel was prepared was (solid dispersion) using PEG6000 and HPMC as carriers, and Carbopol (940) as a gelling agent *(Vasudevan et al., 2011).*

The steps for gel preparation are clarified as follows:

- Mix the drug (100mg) with both (PEG6000&HPMC) in a (2:1) ratio (100mg – 500mg) respectively, and stir well in a China dish.
- Place mixture on the water bath and watch for PEG6000 to melt completely then allow to cool to room temperature.
- Add the cooled mixture to a solvent system constitute of a 1:2 ratio of methanol and dichloromethane, around 3ml, and stir well for good dissolving and mixing.
- Evaporate solvent system to precipitate the drug.
- For Carbopol neutralization, placing the drug in (15%v/w) permeation enhancer (Tri-ethanol amine) a mechanical stirrer to homogeneously mix at high speed was engaged.
- To finalize the procedure, add glycerin and purified water to increase the bulk of the gel or in other words diluent (filler) to make 10g of gel *(Vasudevan et al., 2011).*

The mechanism through which permeation enhancer works is as follows:

- Functions as a co-solvent and enhances the solubility of the drug inside the material as per the "Higuchi model" it enhances the thermodynamic activity of the drug which means a high rate of drug release.
- By decreasing the effect of obstacles that impair the release of drugs easily, it improves the fluidity of skin lipids with layers of keratinized skin.
- It's good to mention that processes that are influencing the release of drugs from gelling agent base are (diffusion and polymer relaxation).

As shown in the table.9, besides Carbopol as a gelling agent, permeation enhancers were used in this study different enhancers have been included to see which one will result in the highest rate of drug release, with different percentages or concentrations, including, DMF, DMSO, PEG4000, Glycerin, Tri-ethanol amine, methyl, and propylparaben *(Vasudevan et al., 2011)***.** Figure 12 shows the steps of Chrysophanol formulation via gel formation.

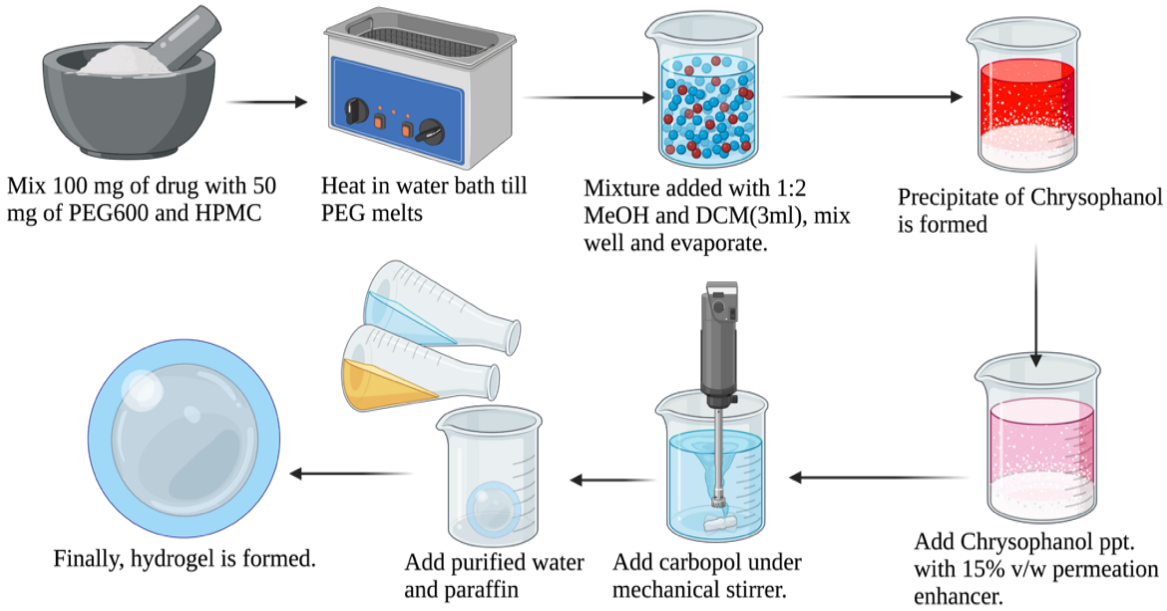

Figure 12: Hydrogel formation technique steps.

Table 7: Composition of gels in different batches (Vasudevan et al., 2011).

Composition	C1 1	C1 2	C1 3	C1 4	C2 1	C2 2	C2 3	C2 4	C3 1	C3 2	C3 3	C3 4
Chrysophanol (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbopol (g)	1	1	1	1	1.25	1.25	1.25	1.25	1.5	1.5	1.5	1.5
DMF% v/w	-	15	-	-	-	15	-	-	-	15	-	-
DMSO% v/w	-	-	15	-	-	-	15	-	-	-	15	-
PEG 400% v/w	-	-	-	15	-	-	-	15	-	-	-	15
Glycerin % v/w	10	10	10	10	10	10	10	10	10	10	10	10
Triethanolamine (ml)	2	2	2	2	2.5	2.5	2.5	2.5	3	3	3	3
Methylparaben (w/v) ml	2	2	2	2	2	2	2	2	2	2	2	2
Propylparaben (w/v) ml	1	1	1	1	1	1	1	1	1	1	1	1
Deionized water to produce (g)	10	10	10	10	10	10	10	10	10	10	10	10

3.3.3.2 Chrysophanol novel formulation (Chrysophanol-phospholipid complex) according to (Singh et al., 2013) study

Apropos of formulations of Chrysophanol particularly in the oral route a big boundary is hampering its bioavailability which is its poor water solubility that apparently is affecting its pharmacokinetics, especially absorption, and distribution *(Singh et al., 2013).*

So for this purpose utilization of pharmaceutical colloidal systems like (Nanoparticles, microemulsion, and solid dispersion.) are involved as a study aimed at improving the hydrophobicity of Chrysophanol was capable of successfully forming Chrysophanol phospholipid complex (CPC) lipid-based complexes were preferred as these form stable complexes with various guest (*Singh et al., 2013).* molecules and drugs of interest subsequently CPC was formed and evaluated by various tests. The method used to make the complex, refluxing was performed, as lipid, part phosphatidylcholine was used with Chrysophanol at a ratio (1:1) in a round bottom flask with a capacity of 100 ml, 20 ml of dichloromethane with both drug and phosphatidylcholine reaction was carried on for five hours, with the use of magnetic stirrer reaction was performed at 45-50°C, next step was condensing the proceeded solution to 2-3 ml subsequently n-hexane was added for purpose of precipitation, followed by the collection of the resultant compound, filtering it, washing it, lastly drying it under vacuum and placing in airtight containers to preserve it. The steps of CPC formation are illustrated in figure 13.

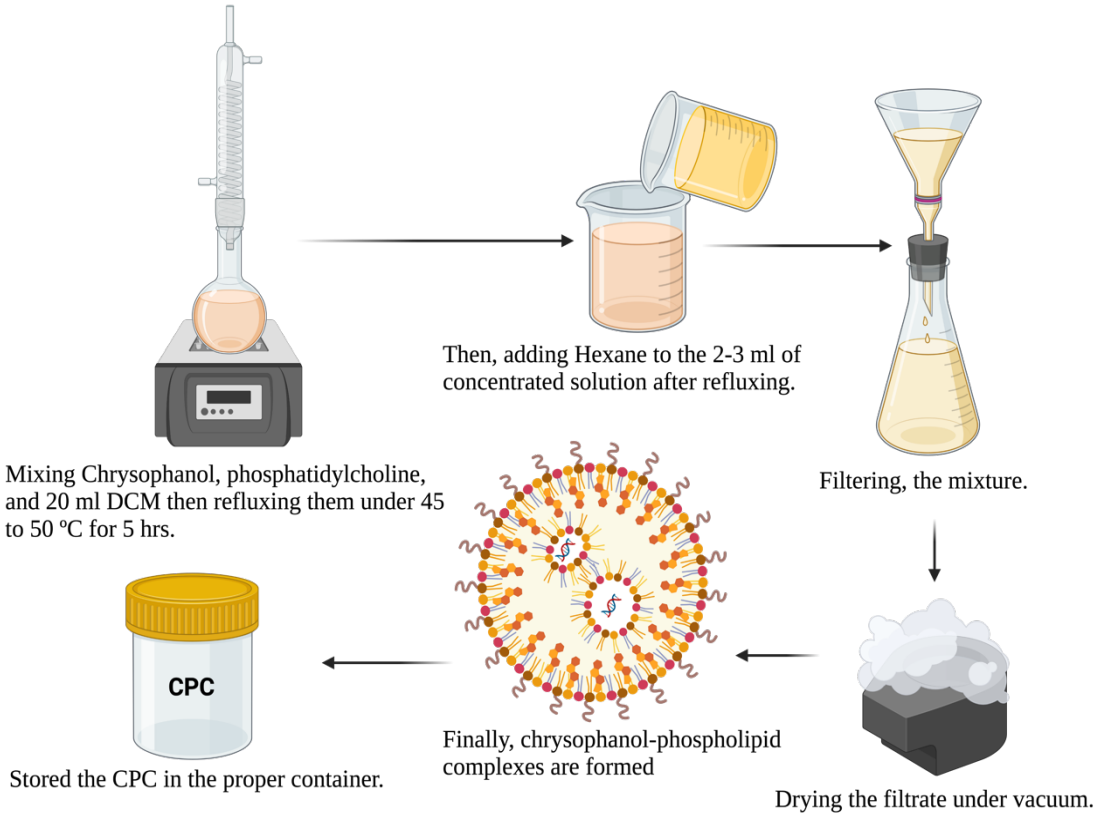

Figure 13: The steps of CPC formation.

3.4 Paclitaxel

Taxol, TM, or PTX are all other names for paclitaxel a component in the Taxane family, composed of 3 cycles (tricyclic) that is a diterpene obtained from the bark of the tree *Taxus brevifolia* or pacific yew tree that is one out of three achievements in the 1990s being considered as one of most potent, efficacious and successful from commercial aspects in managing and treating cancer either advanced or refractory. From 1977 to 1992 through three clinical trials (I-II-III-) Taxol has been reported as effective and beneficial influence on cancer in the ovary, breast, uterus lung… etc *(Yan-Hua et al., 2020).*

There are two preparations for paclitaxel, Taxol and Abraxane the former is based on a 1:1 (v/v) mixture of polyoxymethylene castor oil or called cremophor which is the actual cause of many side effects of the Taxol preparation including hypersensitivity reactions, peripheral neurotoxicity, so a new formulation free from chromophore was synthesized, namely Abraxane even though it's still not apparent whether Abraxane can act against MDR tumors, indicating the necessity of a new paclitaxel formulation to be discovered *(Soto and B., 2022).*

3.4.1 Pharmacological activity of Paclitaxel

The most familiar Pharmacological use of paclitaxel as a glycoside is anti-cancer activity.

3.4.2 Anticancer effect and pharmacological mechanism

Prominently, PTX controls the cell division and mitosis and controls DNA repair as well, throughout the process of mitosis or meiosis the microtubules are forming tubules to enhance the division of chromosomes, Taxol is selective for the beta subunit in the tubulin protein and contributes to their polymerization, this ceases the cell functioning, leads to profound mitosis and consequently results in the death of cancer cell *(Liu et al., 2020).* Unlike other antineoplastic agents, PTX does not intrude with normal division, only interfering with tubulin and stabilizing them in a way that does not allow its depolymerization. Also, the time during which the drug remains in the cell is 20 hours which is adequate to inhibit tumor growth *(Yan-Hua et al., 2020).*

3.4.3 Paclitaxel formulations

Different techniques for paclitaxel formulations are mentioned in figure 14 **(Liu et al., 2020)**

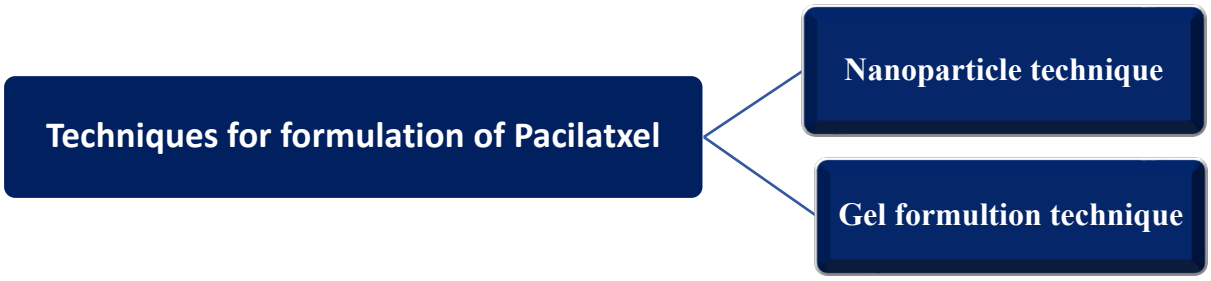

Figure 14: Different techniques for paclitaxel formulations.

3.4.3.1 Paclitaxel nanocrystals for overcoming multidrug resistance according to (Liu et al., 2020 study)

A study aiming at formulating a new dosage form to overcome the resistance of cancerous cells which is namely referred to as (multidrug resistance) resulted due to the action of p-gp or (para-glycoproteins) by restraining accumulation of anticancer drugs in adequate concentration at cancerous cells, as its conducted in this investigation, by utilizing (TPGS) as a stabilizing agent and to inhibit the action of P-gp which is the main reason why such surfactant is chosen among others, another feature is the capability of TPGS to function even at concentrations below the CMC beside its safety in medical applications as its obtained from vitamin E, in addition, its inert and not exhibiting any interaction neither with excipients nor with drugs *(Liu et al., 2020)*.

3.4.3.1.2 Methods of Paclitaxel nanocrystals for overcoming multidrug resistance according to (Liu et al., 2020 study)

The method (stabilizing nanocrystals) (SNC) was used to synthesize nanocrystals, firstly both PTX and TPGS were dissolved in chloroform at a ratio of (1:1 – 1:5) by flowing nitrogen gas through the solution steadily chloroform evaporated resulting in precipitation of both PTX and TPGS later to ensure that precipitate is fully free from chloroform desiccator for 2-4 hours under vacuum was used, hydration was next step with water and vortex, the procedure ended with sonication for 10-15 minutes in a bath sonicator.

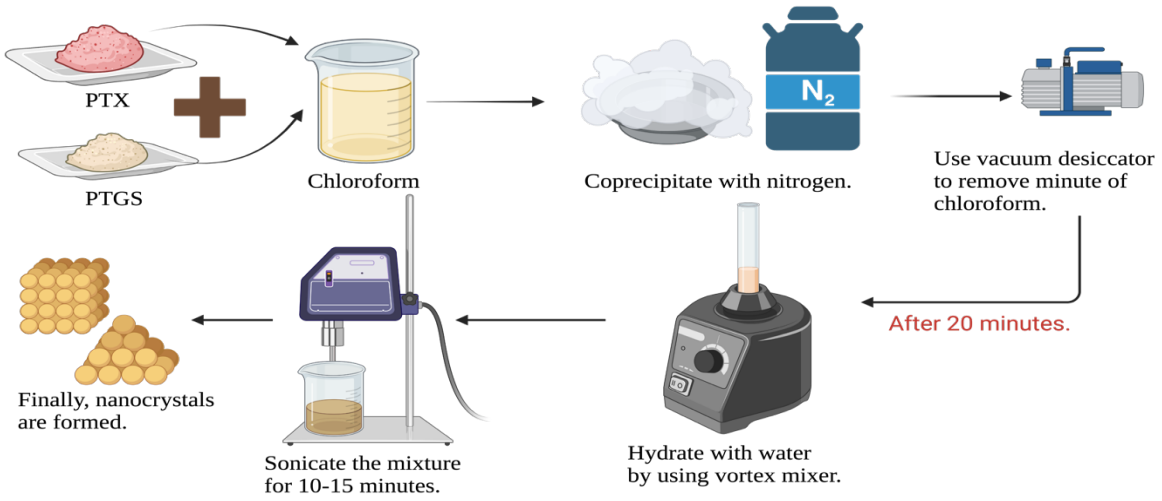

Figure 15: The steps of nanocrystal formation from PTX.

3.4.3.2 Paclitaxel hydrogel formulation (the inhibition of tumor growth and metastasis by self-assembled nanofibers of Taxol) according to (Wang et al., 2012)

Huaimin Wang et al. conducted a study attempting to formulate a hydrogel by process of hydrolysis that can be used either topically or injected into solid tumors to suppress the growth and spread of tumors also the merit of this formulation is that topical application will lead to less concentration of drug in the blood means decreasing side effects and improve tolerance, API used was a Taxol derivative (Taxol-SA-GSSG) (*Wang et al., 2012).*

3.4.3.2.1 Method of Paclitaxel hydrogel formulation (the inhibition of tumor growth and metastasis by self-assembled nanofibers of Taxol) according to (Wang et al., 2012)

Method of preparation included, the usage of 20 mg of the Taxol derivative with 2.2 equivalent amount of sodium carbonate (Na_2CO_3) mixed and dissolved with 1 ml of PBS buffer (pH=7.4), for the gel to be formed it requires a temperature of 37°C for about 12 hours also when the gel is placed in a syringe and injected out of it, obviously its seen how gel will re-formulate following 5 minutes. Figure 16 is illustrated the steps of hydrogel formation from paclitaxel derivative.

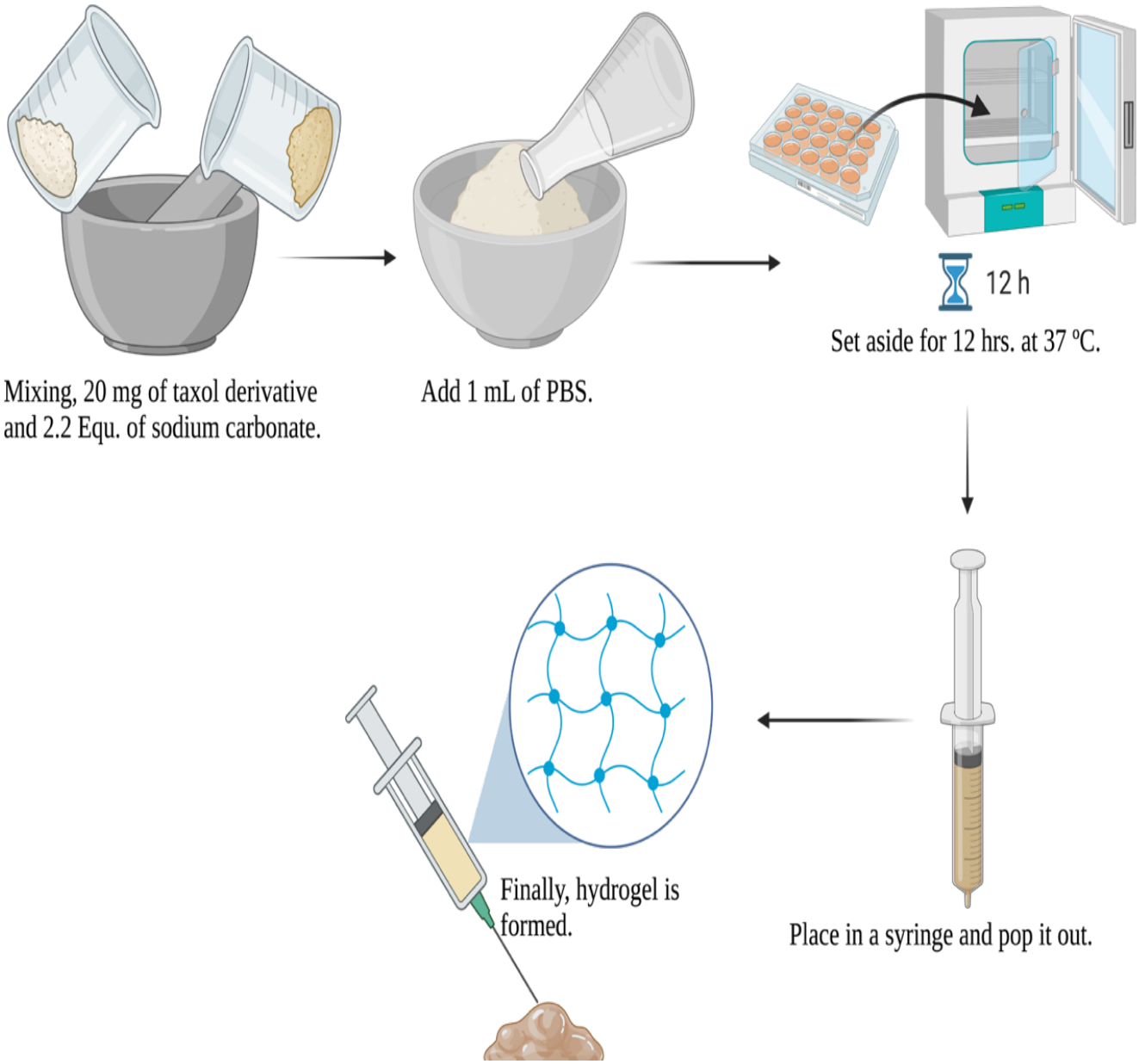

Figure 16: Hydrogel formation steps from paclitaxel derive.

Chapter-IV

Material and methods

4.1 Searching method and the literature that is used in this article

Databases, both online and offline, were used to collect data and information. We benefited from a variety of resources, including the internet and numerous books in my university library. The following online databases were used in the creation of this article:

- ***The Google Scholar***
- ***PubMed***
- ***Scopus Science Direct***
- ***EBSCO Web of Science***

We gathered the information and data for our review article from the databases mentioned above as well as by searching with the right keywords that are themes and synonyms of those topics. All of these sources were utilized because they were all published after the year ***2000***. ***39200*** studies were accessible on Google Scholar when we searched for our issue, however, we only chose 8 research because only those 8 studies fit our criteria.

4.2 Style of searching the terms or keywords

The most crucial stage in creating any article is learning how to search for themes and locate desired articles. Every day, we might employ a variety of techniques or different web search interfaces. Boolean operation is one of the best search-related design patterns. Convenience words are used as conjugations by Boolean operators to join or exclude keywords and terms in a search; these words are utilized in searches using this approach and include ***(AND, OR, NOT, or AND NOT)***. Because this method of searching also saves time and effort by removing irrelevant results or research, using the phrases that belong to it leads to more focused and productive outcomes. For example, when searching for types of glycosides and formulation of different types of glycosides, we wrote (Glycosides OR Formulation techniques)

4.3 Inclusion Criteria & Exclusion Criteria

First, understanding "What are inclusion criteria?" is crucial. Furthermore, "What are exclusion criteria?" The characteristics of the sample population and the data that must be included in your study are known as the inclusion criteria. For example, the data or studies that are included in articles whose publication dates begin in 2000, and this study that the formulated products are lipid soluble.

Exclusion criteria are characteristics of the sample population and data that, if included in the study, could skew the findings. For example, this research excludes water-soluble goods because our formulation methods are employed for water-insoluble medications.

4.4 Analyzing of Date

To ascertain the formulation's effectiveness with various kinds of glycosides, this review article was acquired. There are several data that illustrate the properties of a certain drug before and after formulation. For a convincing interpretation of the data, we evaluated these data in various charts and tables. As well as many software programs are used in this systematic review like Zetoro program for analyzing the researches that we used, and for removing the duplicated articles.

Chapter-V

Result and Discussion

5.1 Analyzing of different studies

In the result of searching for (Glycosides formulations), about (58,1000) articles or abstracts are extracted. From these (58,1000) resulted articles, the best types of glycosides were selected for formulations which were (Garcinia, Sennoside, Paclitaxel, and Chrysophanol) due to their pharmacological activities in treating different types of cancers, and their articles authors and journals are more reliable than others.

In the next step, for each glycosides formulations separately were searched, for instance during searching for (Garcinia formulations) (16,100) articles were resulted, for (Sennosides formulations) (3,250) articles were resulted, for (Paclitaxel formulations) (121,000) articles were resulted, and lastly for (Chrysophanol formulations) (4,330) articles were resulted.

Then, the searching process were customized from the publication year from (2010) to (2023). After customization for (Garcinia formulations) (14,700) articles, for (Sennosides formulations) 1,880 articles, for (Paclitaxel formulations) (27,100) articles, and for (Chrysophanol formulations) (3,360) articles were extracted. Then the free software was used to remove the duplicate researches, this software is called Zetoro program which is a free program to manage academical articles.

For garcinia glycoside formulations from (14,700) articles only (87) articles were selected, for sennoside formulation from (1,880) articles (43) articles were selected, for paclitaxel formulation from (27,100) articles (94) articles were selected, and for Chrysophanol formulation out of (3,360) articles (55) articles were fitted to our project.

The selection of this articles among of this large numbers of articles based on some criteria, such as the highest number of citations, the most reliable publisher journal, open sources articles and availability of completed data. After using the ***Zetoro program***, for garcinia formulation (72) articles were duplicated out of (87) articles, for sennosides formulations (39) articles were duplicated out of (43) articles, for paclitaxel formulations (29) articles were duplicated out of (94) articles, and for Chrysophanol formulations (40) articles were duplicated out of (55) articles.

Finally, among these (15) remained articles of garcinia formulation (2) articles are selected, these (2) articles for topical dosage form were selected because among of these (2) articles their products were used for cancer treatment, and the remained articles for sennoside formulations,

and among these (4) articles we selected (1) conventional technique of oral formulation and (1) advanced technique that used for colon cancer treatment. Again, for paclitaxel among (65) articles only (2) articles are selected, another (63) articles are rejected due to a smaller number of citations and incomplete data in the articles, and these two articles that are selected have the largest number of citations.

Out of (15) selected articles of Chrysophanol formulation (2) articles are selected one of them orally for cancer treatment and another one is not used for treating cancer. The process for study selection is illustrated in figure 17.

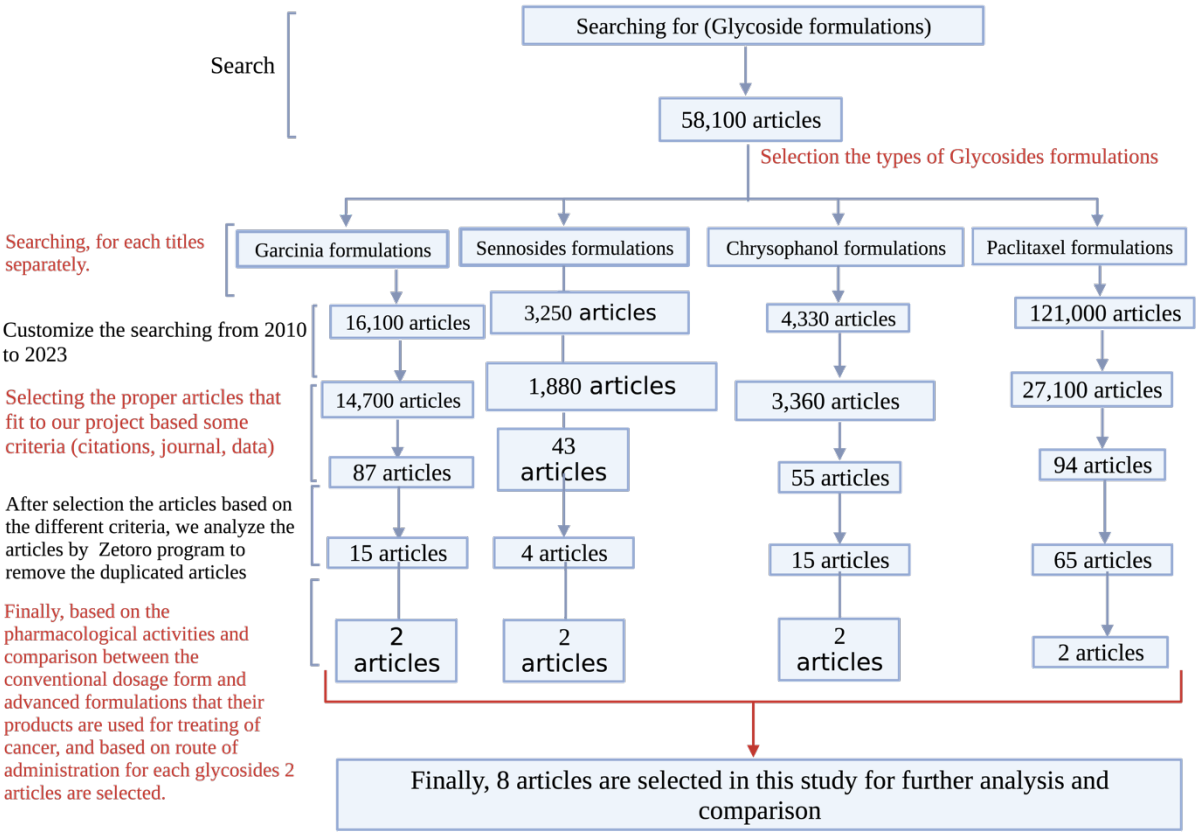

Figure 17: This flow diagram is illustrated this process that used in study selection in the project.

5.2 The characteristic of the produced dosage form

In this study this formulation techniques are selected that their products are easily administrated without any professions and skills such as topical and oral dosage forms. Anticancer properties and selectivity are the basic characteristics of the formulation that formulated through advanced technique, such as nanoparticle, encapsulation or fabrication methods. The products that

formulated by conventional techniques are not selective and they have not anticancer properties, but the conventional techniques are mentioned in this study for proving that formulation techniques are the key factor for achieving different pharmacological activities.

5.3 The formulation techniques were used from different studies to comparison

All of the 10 studies and their different techniques for formulation of different dosage forms are shown in table 8. In this section through these tables, all different techniques are comprised separately about their extracted drug that formulated, steps of formulation, consumed materials and their results.

Table 8.1: Summarization of gel formulation technique.

Materials	Methods	Results
• Extract of Garcinia mangostana L. fruit pericarp, which is extracted by using 70% of ethanol. • Radical 2,2- diphenyl-1-picrylhydrazyl/DPPH • 10% of Ethanol. • Methanol. • 2% of Sodium carboxyl cellulose • 0.1% Methyl paraben • Phosphate buffer saline pH 7.4 • 100% deionized water	• **Gel formulation** sodium carboxymethyl cellulose (CMC-Na), ethanol, methylparaben, and 100% deionized water make up the gel base. Deionized water is combined with CMC-Na, which is subsequently hydrated with 750 rpm of agitation overnight. Finally, methylparaben is added. In order to create a uniform gel formulation, the APA, which is 20% Garcinia mangostana L. fruit pericarp extract, is added to the gel base that was previously prepared with continuous agitation or stirring.	**Gel Evaluation after formulation** • After testing of formulated gel for its scavenging activity, same of extract of Garcinia mangostana L. fruit pericarp scavenging activity is resulted, it means the scavenging activity of extract or pure drug is not decreased. • Formulated gel is stable or unchangeable on the skin for 24 hours which is necessary for in vivo release and vitro skin penetration. • Again, DPPH scavenging activity method is used to detect in vitro release of active ingredient from the gel base, as shown in figure X. • The skin permeation evaluation is conducted on the shed snakeskin which is used as skin membrane, and the result of the test detected that pure drug is more retain on the snakeskin than gel formulation, which is meaning that gel formulation has more membrane permeation capacity.

Table 8.2: Summarization of encapsulation method.

Materials	Methods	Results
• Mangosteen pericarp. • Sodium biphosphate. • Potassium biphosphate. • Ethanol. • Ethyl acetate. • Xanthan gum. • Span 80 and Tween 80. • Virgin coconut oil.	**Extraction of mangosteen** The powder is macerated in ethanol for a week. After extraction, the dry power must be fractionated by using an equal volume of ethyl acetate and water. The mangosteen-rich ethyl acetate fraction is dried in rotary evaporation to produce dry mangosteen extract powder. **Nano-emulsion preparation** • The virgin coconut oil, mangosteen extract and surfactants which are Tween 80 and Span 80 are oil phase. Combination of the surfactants are requested in order to hydrophilic and lipophilic balance in formulation. • The mangosteen extract dissolved in virgin coconut oil by the ratio of 1:2.2 (mg per mL), and homogeneous solution is obtained by stirring at 750 rpm. The oil phase is prepared by mixing virgin coconut oil and mangosteen extract with Tween 80 and Spas 80 under stirring 500 rpm for 10 min. • The nano-emulsions are formed by mixing the oil phase with distilled water by the ratio of 1:1.04 (v per v) and stirring at 750 rpm util they will be mixed well. To homogenize coarse emulsion the high-speed homogenizer, Ultra Turrax, T18 are used for 15 minutes under 6000, 8000 and 10000 rpm.	• The extract sample solution is determined by UV under 316 nm. For determining existing of alpha mangostin in sample solution. • Alpha mangostin constituent in the formulation is 0.012% (w/w), while 0.020% (w/w) extracted sample is added to the nano emulsion. • In the result, the best ratio of virgin coconut oil to surfactants is 1:1.4 in 0.01% (w/w), in order to stable formulation. • The best surfactants in order to stable formulation are Tween 80 and Span 80. • Droplet size and Zeta potential can affect the permeability and penetration the drug, and the most proper droplet size and zeta potential are obtained when the Tween 80 and Span 80 as surfactants are used, homogenizing speed between 6000 to 10000 rpm, and ratio of virgin coconut oil to surfactants is 1:1.4 in 0.01% (w/w).

Table 8.3: Summarization of wet tablet granulation technique.

Materials	Methods	Results
• Senna leaves • Lactose-MCC complex • N-propranolol	• Mixing of lactose-MCC, Senna extract, n-propranolol. In the result coherent mass of granules is formed. • Screening or sieving of the produced mass of granules by special sieve 8 to 10 times, in order to obtain uniform mass of granules. • Drying the sieved granules at 60ºC by hot air oven. • Again, sieving or screening the dry granules 20 times. • Lubricant is disintegration agent in order to disintegration of the tablet when contact with medium of fluid. And uniform of flow in the bunch and die. • Again, mixing the dry granules and the lubricant by blender. • Tablet preparation is obtained by special instrument, for instance bunch and die.	• In the result, extraction of senna leaves by maceration technique in 70% hydroalcoholic solvent yields the highest amount of Sennosides. For instance, extraction of sennosides by 50% v/v water to ethanol, 80% v/v, 100% v/v yield lesser amounts of sennosides than 70% v/v. • We cannot detect sennoside B by TLC, but can be detected by HPLC because it is more sensitive than TLC. • This tablet that formulated by this technique is not is used for cancer treatment because it is not more selective. • This tablet that formulated or produced by this technique mostly used for purgative and gastrointestinal problems.

Table 8.4: Summarization of fabrication technique.

Materials	Methods	Results
• Cetyltrimethylammonium (molecular weight is 364.45 g/mole). • Silver nitrate (molecular weight is 169.87 g/mole). • Safranin (molecular weight is 350.85 g/mole, and must be water soluble). • Deionized water, for preparing stock solution of these three previous chemicals. • Inorganic electrolytes, such as NaCl, NaBr, NaI, NaNO3, NaOH, and Na2SO4. • Organic solvents, such as methanol, ethanol, chloroform, and diethyl ether. • HCL, prepared under analytical grade. • pH maintenance, such as HCL and NaOH solutions. • Silver nitrate solution must be kept in dark place to avoid oxidation.	• **Extraction of sennoside A from fresh leaves of senna which is Cassia angustifolia Del.** Senna, or Cassia angustifolia, is first harvested for its fresh leaves, which are then washed twice—once with tap water and once with double the amount of distilled water—to remove dust and other foreign substances. The leaves are collected, washed in water to remove dust and other impurities, and then dried in the sun. 10 grams of the dried leaves are then added to a stoppered conical flask containing 200 mL of double-distilled water, and the mixture is heated at 80ºC for 30 minutes while being constantly stirred and heated in a water bath. After being heated in a water bath, the filtrate must cool to room temperature before beginning to be filtered using Whatman filter paper to remove the waste from the leaves. To create a dark yellow chemical, the obtained fresh extract must be treated using a rotatory evaporator under vacuum at 80°C temperature. Sennoside A and B, aloe emodin, and Rhein glycoside are all components of the senna leaf extract. Finally, using particular purification procedures, sennoside A is separated from the resultant dark yellow substance. • **Fabrication of Ag/sennoside A nanoparticles** Sennoside A, which was previously isolated, is introduced to a conical flask containing 5 mL of an aqueous solution of AgNO3 (0.01 mole/L) and 1.4x10-4 moles of sennoside A (1.4x10-4 mole/L). Sennoside A and AgNO3 must be combined, and the mixture must then be continuously stirred by a magnetic stirrer at 1500 rpm for 30 minutes. When the mixture's color changes from yellow or orange to dark brown, this indicates that the (Ag+) ions have been reduced into metallic silver (Ag^o). To produce silver nanoparticles, the resulting dark brown color mixture was centrifuged at 15000 rpm for a half-hour at 25 ºC. After being created, the silver nanoparticles must be dried at 80 °C and then stored at room temperature in a dark environment. To achieve the best delivery method to the colon or to treat digestive issues and anthropoid's infections in the colon, the generated silver nanoparticles are loaded with sennoside A by centrifugation	• In order to produce stable nanoparticles by fabrication technique optimum concentrations of extracted sennoside, Ag+ ions, and CTAB are requested. For instance, sennoside concentration is 120.78 mg/L, Ag+ ions concentration is 75.5 mg/L, and CTAB concentration is 921.1 mg/L. • When water, sennoside, CTAB, and Ag+ are mixed. In the result phenolic -OH group of sennoside is bonded to the Ag+ ion to reduce Ag+ to Ag^o.

Table 8.5: summary of formulation and in-vitro evaluation of Chrysophanol gel.

Material	Method	Results
Carbopol-940 Chrysophanol PEG6000 HPMC Methanol dichloromethane	• 100mg drug added to 100mg mixture of both carriers (PEG6000&HPMC) (2:1) in a china dish mix well • Heat using water bath until PEG thoroughly melts • Let the mixture cool till reaches room temperature • Prepare& add 3ml of solvent system that encompasses methanol and dichloromethane • Cautiously evaporate solvent system to get precipitate • Gather all precipitate and mix with permeation enhancer15%w/w associated with constant mixing • Lastly add glycerin and water to make up final volume of the gel	Resultant formulation was successful in terms of stability, homogeneity, pH was in suitable range for skin application (between 6.5-6.9). it passed the content uniformity tests results revealed 98.7-99.6%. also its good to mention that no skin irritation or reaction was observed as illustrated by the study. On storage no deterioration, change in pH, viscosity or homogeneity was observed.

Table 8.6: summary of preparation of Chrysophanol-phospholipid complex.

Material	Method	Result
Chemicals: Chrysophanol Phosphatidylcholine Dichloromethane n-hexane Equipment: Round bottom flask Magnetic stirrer Filtering equipment Vacuum drying	• Place both chrysophanol and phosphatidylcholine in a 100ml capacity RBF with dichloromethane as a solvent • Utilizing a magnetic stirrer, at 40-45 Celsius degrees refluxing was performed for five hours • Concentrate the outcome of previous step to 2-3ml • Obtain precipitate by addition of adequate quantity of n-hexane • Gather, wash and filter product • Dry using vacuum drying technique • Preserve In unassailable containers.	Regarding encapsulation efficiency, as UV spectrophotometry has displayed 91%w/w was observed, also in DSC neither of excipients showed any thermal sign however an endothermic peak was noticed by phosphatidylcholine, in addition X-RPD, an index of crystallinity, revealed absolutely no intensity of peaks in CPC means absence of crystallinity beside its porous, rough texture and fluffy characteristics

Table 8.7: summary for PTX nanofiber preparation by method of stabilization of nanocrystals (SNC).

Material	Method	Results
Chemicals: • Paclitaxel • Tocopheryl polyethylene glycol 1000 succinate (TPGS) • Chloroform • Nitrogen gas Materials: • Vacuum desiccators • Sonicator (bath-type)	• Solubilize both of TPGS and PTX in chloroform • Evaporate chloroform to get precipitate using nitrogen gas • To ensure complete absence of chloroform in ppt., utilizing vacuum desiccator for 2-4 hours. • Using a vortex mixer after 20 minutes hydrate with water • Sonicate for 10-15 min. using bath sonicator to synthesize the nanocrystals.	TEM imagen's results illustrated identical, average and baculiform size and shape. Formulation had substantial capability in tumor growth inhibition and more importantly, efficiently combated with cells highly releasing P-gp which Taxol and other formulation could not beat-off in NCI/ADR-RES cells also displayed triumphant and pleasing results in other studies like antitumor efficacy, dose dependent assay and others as mentioned in previous sections.

Table 8.8: summary of reparation of paclitaxel self-assembled nanofibers.

Material	Method	Results
Chemicals: Sodium bicarbonate PBS buffer Taxol-SA-GSSG (paclitaxel derivative)	• Add 20mg of Taxol-SA-GSSG with 2.2 equivalents of sodium bicarbonate together and dissolve using 1ml PBS buffer • Leave mixture at 37 Celsius for 12 hours until gel is formed • Aspire gel into syringe and inject it out from it to see the reproduction of the gel following 5-minute period.	It was observed how the Taxol derivative will regenerate hydrogel via ester-linked hydrolysis process, molecule passed gelation test through leaving it at two different temperatures both room and body temperature. Yielding57% and 95.4% subsequently. Fatal dose was roughly 7.5 times higher than that of Taxol indicating more safety. Appearance was harmonic intertwining of the fibers also concerning pharmacological efficacy.

5.4 Comparison between Gel formulation technique and fabrication technique for preparing topical dosage form of garcinia Glycoside

Dosage forms for topical use, such as cream, gel, ointment, and spray. The majority of the time, topical dose forms are used to treat skin conditions brought on by radiation or microbiological agents. They are also occasionally used to treat localized discomfort.

We only discovered topical formulations using gel, nano-emulsion, or encapsulation techniques when looking for the topical dose form of Garcinia glycoside.
Garcinia mangostana L. formulations are made using both methods. Topical gel made from Garcinia mangostana L. can have antioxidant effects. These medications that are applied topically and contain antioxidant properties are an important class of medications or agents that can stop or lessen the degree of UV-induced skin damage, which can occur in older adults at times. Mangosteen extract is also encapsulated in virgin coconut oil-based nano-emulsion for the topical formulation, which is used to treat skin infections caused by fungi, viruses, tumors, and bacteria. Mangosteen is one of the glycosidic components of Garcinia mangostana L. This section generates the question, ***"Could mangosteen be formulated using gel formulation?"***
Drug formulation methods such as encapsulation or nanoparticles can produce stable dosage forms that are resistant to bacteria, fungi, and viral agents.

Certain types of skin cancer are treated topically, and the medications used to treat malignant growths must be highly selective for their targets. "NO" is our response to the query. Because mangosteen glycoside exhibits anti-cancerous, antiviral, antibacterial, and antifungal activity, we were unable to formulate the mangosteen extract from Garcinia mangostana L using the gel formulation method. Therefore, nano-particles or encapsulation meth uses must be utilized in formulation to create a component with this property because medications delivered by nano-emulsions are resistant to bacterial, fungal, and viral agents.

Additionally, they are selective when applied topically to treat skin tumors. On the other side, a medication or product can be created using the gel formulation process that is more spreadable, penetrable, and retainable in the shed snakeskin. However, a basic gel formulation product cannot be selected for skin carcinoma cells and cannot be durable against microbiological agents *(Kuswahyuning et al., 2019)*, *(Mulia et al., 2018).*

5.5 Comparison between wet granulation technique and fabrication technique for preparing oral dosage form of sennoside A glycoside

Various research suggests that sennoside an oral dose form could be created for a glycoside. The most common method for making sennoside glycoside is the traditional wet granulation method, and we've already covered the stages involved in this method.

The desired tablet is typically employed for purgative technique in this conventional method, which is also known as the wet granulation method or conventional tableting method of Sennoside A. Sennoside To boost gastrointestinal absorption, increase bioavailability, and minimize toxicity by a limited amount, a glycoside formulation using wet granulation technology may be used.

Sennoside A has a wide range of pharmacological effects and uses, including the treatment and prevention of constipation, the reduction of body mass index, the treatment and prevention of diabetes, the prevention of fatty liver disease, and the reduction of inflammation and colon cancer treatment. On the other hand, it has gastrointestinal negative effects, like colon cancer, which is brought on by prolonged usage of sennoside A, which is created using the wet granulation technique, at high doses (2021; Yueqiu Gao).

The creation of Ag/sennoside A nanoparticle is another sophisticated technology employed for sennoside-A oral formulation. This cutting-edge strategy is better than the traditional approach since it has the potential to lessen negative effects more than the traditional approach. The most selective formulation of sennoside A glycoside may be made using modern techniques, and because of its selectivity, sennoside A may be utilized to treat colon cancer.

Sennoside A can be synthesized using the Ag/Sennoside A nanoparticle production approach and thanks to its excellent stability, it can be utilized as an antibacterial and antifungal agent that is meant to treat GIT infections. after ingesting oral formulations of Ag/Sennoside nanoparticles, which were created using cutting-edge technology. In the GIT, sennoside A is degraded to produce the antibacterial compound rho-9-anthrone.

As a result, this version of sennoside A is typically utilized to treat colon infections and digestive disorders *(Dhoble et al., 2019), (Al-Ghamdi et al., 2020).*

5.6 Comparison between gel formulation technique and complexation technique for preparation of Chrysophanol formulation

Various formulations have been synthesized in different methods such as solid dispersion, microemulsion, liposomes…etc.

With Chrysophanol, major challenging task is to enhance its bioavailability as well as absorption and solubility due to its low hydrophilicity in this particular review article two

methods were chosen amide numerous formulation techniques. Formerly phospholipid incorporation method in an attempt to increase solubility as illustrated in previous sections by refluxing, results exhibited good encapsulation efficiency (91%w/w) increasing amorphousness, formulation displayed 83.67% release following 12 hours of administration that reveals up to some extent that it can act as sustained release formulation, in my humble opinion this method despite successfully achieving desired targets it possesses demerits like, typical encapsulation limitation involving leakage of drug out of complex, expensiveness, difficulty in manufacturing, sterilization problems and so on.

Meanwhile, second technique discussed was gel formulation by solid dispersion technique that used carbomer resin as base for the gel and to strengthen the study and ensure which concentration is most effective, different concentrations are studies, as it's known Carbopol has the feature of changing its phase in diverse pH medias, so to stop this process its neutralised by trirthanol amine.

To ease and optimize drug release, different concentration of permeation enhancers was implemented to increase thermoactivated of gel resulting in enhanced drug release. Good aspects related to this gel is that it can be administered in different routes but same formulation, like, orally, rectally, ocular, cutaneous as well as subcutaneous this is index for higher chances are there its used for different patients (age categories), diseases as well as preferences, also sustained manner of release has been observed making it desired dosage form for majority of patients means less dosing intervals and less dose administration in turn less drug interaction, more compliance.

In my lights, drug content in case of gel was higher (98.7-99.6%) compared to previous CPC, encapsulation efficiency 91%w/w even though result is good and adequate, however 9% is not sufficiently encapsulated, signifying that leakage possibility is there *(Vasudevan et al., 2011), (Singh et al., 2013).*

5.7 Comparison between nano particles techniques and Gel formulation technique for paclitaxel formulations

Both implemented methods are involved under the umbrella of nanotechnology, with differences and resembling points, as an instance both methods attempt to deliver PTX in form of (nano-sized) dosage forms despite differences in method of preparation and type of sole

excipients being implemented. In the nanofiber hydrogel method, the drug form is not pure paclitaxel but commercial Taxol, type of substance used as main excipient which was succinic acid and oxidised glutathione, the reason behind why these two were used, is that both can be safely used on living organisms, these are commercially available and easy to obtain and the latter (GSSG) is hydrophilic this eases the solubility.

The method in here is self-assembling process it's easy to perform not complicated at all, due to hydrolysis process gel s formed and fibbers intertwine supporting so. second method was utilizing procedure of stabilizing nanocrystal, only TPGS was utilized no other excipients, it was particularly selected due to its potent capacity to inhibit P-gp, safe to be used in-vivo which is mutual with previous excipients (SA&GSSG) also due to its high hydrophilicity enhances overall formylation solubility.

As per parent papers both formulations exhibited success however none could be claimed as definitely better or superior, as each has unique characteristics such as, the nanofiber hydrogel has wide therapeutic index (Fatal dose was 7.5X higher than that of Taxol) also can be administered either locally or into desired site, while in nanoparticle method it's not illustrates. However, nanoparticles are advantageous in terms of drug loading capacity as only two components (drug+TPGS) are involved so up to 50% drug can be loaded also sustained release manner is present and overall, its cost-effective (*Wang et al., 2012), (Liu et al., 2020).*

Chapter – VI
Discussion and Recommendations

6.1 Discussion

There are many subjects to discuss in the collection of (10) different studies on the formulations of different types of glycosides.

- First, are there these products that we mentioned in the market? if there are not available, what are the reasons that these products or these formulations are not available in the markets?
- Second, it is clear that for most of each mentioned glycosides the conventional techniques and the advanced techniques are mentioned. Which one has more side effect?
- Third, what are the recommendations and instructions for mentioned glycoside formulation, if they are used?

6.2 Mentioned glycosides in the markets

In the markets, a large numbers of Garcinia mangostin tablets and capsule are available that intended orally as a dietary supplement.

These dietary supplements that commercially available in the markets used for weight balancing, controlling of appetite, and reducing of cholesterol. As well as these dietary supplements of Garcinia mangostin are formulated by SDS. Extracted Xanthone are available in the markets that can be formulated by encapsulation technique to treat cancer diseases. Unfortunately, there is a gap in the markets for having topical formulation of garcinia to treat skin disorders, and we hope that the industrial pharmacists and the investigators tray to bring the garcinia mangostin gel in the markets by their advanced investigation because garcinia mangostin gel is one of the most potential and safest products for treating of skin condition by radiation according to *(Rina Kuswahyuning's study).*

Sennoside tablets that formulated by wet tablet granulation technique are commercially common in the markets, which are used to support bowel and digest tract health, constipation, digestion, ingestion, fever and decreasing body weight.

Another sennoside formulation that commercially exists in the markets is senna cream which is used for cosmetic purpose, and there is not specific study on the sennoside formulation as a topical dosage form, we are suggesting for doing the studies on the formulating of topical dosage forms from of sennosides because the herbal products are better than the synthetic or the chemical products.

Another novel formulation for Sennoside is fabricated sennoside tablet that used for colon cancer according to *(Abdulrahim F.A Aisha's study).*

But the fabricated sennoside is not available commercially, because the researches till now is not sufficient to prove and to accept the WHO and FDA for marketing of fabricated sennoside for cancer.

The newest approaches for formulating of Chrysophanol which are gel dosage form and tablet by complexation technique with phospholipid. Formulation the Chrysophanol through these two techniques are very necessary because through gel formulation technique of Chrysophanol most of the skin infection are cures without using chemical antibiotic, and through complexation technique the herbal field for treating of cancer will be advanced more. So doing more and further researches on these two formulation techniques are essential from the investigators to bring these products in the markets and to serve the population.

The drugs that formulate by conventional technique which is nanoparticle method for producing of Paclitaxel tablet or vial are available commonly in the market, which is used mainly for treating of majority of the cancer types by slowing cancer cell growth. The conventional produced paclitaxel combines with many side effects and adverse effects, we can decrease these side effects and adverse effects by changing route of administration and changing the dosage form of the medicine.

Hydrogel formulation technique is the advanced technique to formulate hydrogel paclitaxel which is not available in the markets. Again, we offered the researcher and the investigator to doing more research on the hydrogel formulation technique to formulate paclitaxel, because it the safest treatment of cancer according to *(Wang et al.'s study in 2012).*

6.3 Comparison between advanced techniques and conventional techniques to formulate the glycosides

The conventional techniques of formulation or classic techniques of formulation are starter method to formulate any products. Surely, any classic method and conventional technique to formulate the drugs may have many side effects and adverse effects, after determining the side effects and adverse effects the researchers and investigators try to find another method that has less side effects and adverse effects as compare to the conventional technique. In table 9 the comparison between these two different types of techniques is explained.

Table 9: Comparison between these two different types of techniques is explained.

Conventional techniques	Side effects of conversional techniques	Advanced techniques	Side effects of advanced techniques
Wet tablet granulation for sennoside	Colon cancer	Fabrication techniques	Isn't caused for colon cancer, may cause nausea and vomiting.
Solid dispersion technique for garcinia	Liver problems, nausea, vomiting and head ache.	Nanoparticle technique	May cause lactic acidosis, may slow down blood clotting, and my interrupt chemotherapy but this technique has more advantage than conventional technique because it can be used as cancer treatment
Nanoparticle technique for paclitaxel	Hair loses, numbness and risk of infection.	Hydrogel technique	Same side effect with conventional but with lesser extent.
Gel formulation technique for Chrysophanol	Less selective may cause cytotoxicity.	Complexation technique	More selective and less cytotoxic.

6.4 Recommendations

In the end chapter of this study, we will request some factors and recommendations to two sides, first to the researchers and second to the medication consumers. We order the investigators and researches to do more study on the herbal drugs and try to replace the chemical drugs and synthetic therapies to herbal and natural drugs, and try to full the markets with herbal drugs.

And we recommend the medication consumers and the individuals, when they become sick try to use the herbal therapies instead of chemical drugs.

Chapter -VII

Conclusion

7.1 Conclusion

In conclusion, the four various types of glycosides that we stated can be used to produce a variety of pharmacological effects, but none of these effects can be attained without formulation techniques and process.

The methods that are consumed to formulate the mentioned Glycosides depend on their nature and the target area for their pharmacological effects.

Sennosides are formulated via wet tablet granulation and fabrication, and the final product can be taken orally.

On the other hand, Garcinia glycoside is formulated through many distinct methods but we explained and reviewed two of them, because these methods resulting in goods that are consumed topically, typically for many severe skin conditions that can be replaced many chemical products that related to many side effects, and unfortunately Garcinia as topical dosage form with numerous of pharmacological activities for the skin aren't available in the markets.

Paclitaxel and Chrysophanol mostly, they are used as anticancer treatment. Chrysophanol can be formulate through complexation technique and gel formulation technique. This product that formulates by gel formulation method can be used for skin infection topically, but the complexation product after formulation is more selective hence it can be used as anticancer agent.

And the last glycoside that we introduced in this project is Paclitaxel which is the most famous glycoside for anticancer activities, also it can be formulate via nanoparticle technique and gel formation technique. Nanoparticle products can be used as an inhibitor for metastasis of cancerous cell like a chemotherapy. In general, glycosides have a solubility problem in the aqueous media of the GIT, which also contributes to a reduction in their bioavailability. This problem is finally resolved by formulating glycosides using various processes.

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APPENDIX

Appendix

In the margins and appendices of this academic project we would like to show some other work that we have done during the writing and preparation of this project, include:

Appendix (1): A paper that we published by the name of (A comprehensive Review on Pistacia Khinjuk Well-Known Medicinal plant), by ***Omji Porwal***, Eron Sulaiman Mahmood Rasul, Halo Fadhil Abbas Qasm, Laza Saadi Mustafa Senjawi, Sachin Kumar Singh, ***Bawan Jalal, Abdulla.***

Appendix (2): An accepted paper from 3rd NTPC, under the title of (A Comprehensive Latest Review on Glycoside), by ***Rozhan Arif,*** Bawan Jalal Abdulla, Kale Bahadeen Othman, Kochi Ari, Omji Porwal.

Appendix (3): An academic poster that generated for the NTPC's submitted abstract, under the title of (Novel formulation approaches for glycosides), by Bawan Jalal Abdullah, Kale Bahadeen Othman, Kochi Ari Ibrahim, Rozhan Arif, Omji Porwal).

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Omji Porwal, Eron Sleman, Halo Fazil, Laza Saadi Mustafa Senjawi, Sachin Kumar Singh, Bawan Jalal Abdulla, A Comprehensive Review On Pistacia Khinjuk Well-Known Medicinal Plant

A Comprehensive Review On Pistacia Khinjuk Well-Known Medicinal Plant

Omji Porwal[1*], Eron Sulaiman Mahmood Rasul[1], Halo Fadhil Abbas Qasm[1], Laza Saadi Mustafa Senjawi[2], Sachin Kumar Singh[3, 4], Bawan Jalal Abdulla[1]

Abstract

Pistacia, a genus of flowering plants from the family Anacardiaceae, contains about twenty species, among them five are more popular including *P. vera, P. atlantica, P. terebinthus, P. khinjuk,* and *P. lentiscus*. Different parts of these species have been used in traditional medicine for various purposes like tonic, aphrodisiac, antiseptic, antihypertensive and management of dental, gastrointestinal, liver, urinary tract and respiratory tract disorders.*Pistacia khinjuk* Stoks (*P. khinjuk*) is an evergreen shrub or tree of the family Anarcadiaceae. This specie is native to Turkey, Syria, Iraq, Iran, Egypt, Afghanistan, India and Pakistan.*P. khinjuk* used as tonic and expectorant, it has been used in cough, fever and asthma.Few investigations have been reported the effect of different crude and isolated compound extracts of *P. khinjuk* on different diseases such as antidiabetic, antitumor, anti-cholinesterase, antimicrobial and antifungal activity. The oil of *P. khinjuk* kernel is valuable oil being used in the pharmaceutical industry. It's mainly composed of oleic, linolenic, palmitic, linolenic, behenic,lauric, myristic and arachidic acid. In addition, oil is considered a valuable source of tocopherols and tocotrienols because the tocols content reported for this oil is much higher than that of common oils. The aim of the present review is to explore the traditional and modern knowledge including the botanical description, ethnomedicinal claims, pharmacognostic parameters, phytochemicals and pharmacological potential of *P. khinjuk*. The comprehensive literature and relevant information regarding the plant were gathered through electronic databases including Google Scholar, Pub Med, Science direct, online open access databases and books from the college library. The review represents consolidated summary in all aspects of plant with a special emphasis on reported phytochemicals isolated from plant and their therapeutic potential. The rearranged data in the form of a single review will be essential in providing updated knowledge to the readers regarding the plant and it will act as a baseline for future exploration of *P. khinjuk*in terms of its phytochemistry and pharmacology.

Keywords: *Pistacia, Pistacia khinjuk* Stoks, Anarcadiaceae, tocopherols, Phytochemicals, Pharmacological potential

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Introduction

Plants are important elements of the universe. They are good sources of natural bioactive secondary metabolites and work as reservoirs of phytochemicals. In a process of photosynthesis plants absorb the sun light and produce high levels of oxygen and secondary metabolites of medicinal importance that are stored in different parts of the plants [1]. Human beings have used plants as medicine, flavouring and recreational drugs for treatment of different ailments with reputation as effective remedies from very beginning of time form thousand years back in history [2]. Large

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Appendix (1): A paper that we published by the name of (A comprehensive Review on Pistacia Khinjuk Well-Known Medicinal plant), by ***Omji Porwal***, Eron Sulaiman Mahmood Rasul, Halo Fadhil Abbas Qasm, Laza Saadi Mustafa Senjawi, Sachin Kumar Singh, ***Bawan Jalal, Abdulla.***

A COMPREHENSIVE LATEST REVIEW ON GLYCOSIDES

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ABSTRACT

Many plant secondary metabolites in nature occur as glycosides. In plants, glycosides are derived mostly from postmodification of the secondary metabolites catalyzed by plant enzymes, glycosyltransferases. Further modifications of the glycosides, such as oxidation, acylation, and degradation, take place frequently. Numbers of biologically active compounds are glycosides. Sometimes, the glycosidic residue is crucial for their activity, in other cases glycosylation only improves pharmacokinetic parameters. Recent developments in molecular glycobiology brought better understanding to the aglycone vs. glycoside activities, and made possible to develop new, more active or more effective glycodrugs based on these findings - very illustrative recent example is the story of vancomycin. This paper deals with an array of glycosidic compounds currently used in medicine but also with biological activity of some glycosidic metabolites of the known drugs. It involves glycosides of vitamins, polyphenolic glycosides (flavonoids), alkaloid glycosides, glycosides in the group of antibiotics, glycopeptides, cardiac glycosides, steroid and terpenoid glycosides etc.

Keywords- *Glycosides, glycosidic antibiotics, Glycopeptides.*

Appendix (2): An accepted paper from 3rd NTPC, under the title of (A Comprehensive Latest Review on Glycoside), by ***Rozhan Arif,*** Bawan Jalal Abdulla, Kale Bahadeen Othman, Kochi Ari, Omji Porwal.

Novel Formulation Approaches For Glycosides

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Background

This project involves a review of the formulation of two important types of glycosides, namely sennosides and paclitaxel. Techniques that make sennosides useful in medicine include wet tablet granulation and fabrication technique. On another hand, the techniques used to formulate paclitaxel are nanocrystal and hydrogel techniques. These two types of glycosides with their sources that will explained are figured in figure (1).

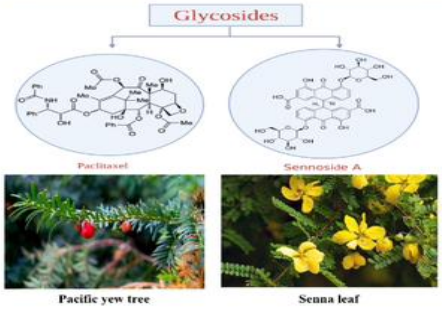

Figure (1): Chemical structures of Paclitaxel and sennoside and their sources which are Senna leaf and Pacific yew tree.

Purpose

Our goal in reviewing glycoside formulations is to further develop, and enrich anticancer drugs from natural sources. Collection, summarization and comparison of different types of glycosides and their formulations in one paper for the convenience of the reader.

Method of Literature search

The following online databases were used for writing this project:

The Google Scholar
PubMed
Scopus Science Direct
EBSCO Web of Science

During preparing of this academic poster (4) main studies were used and reviewed.
Convenience words are used as conjugations by Boolean operators.
Inclusion criteria are these studies that about formulation of insoluble drugs.
Exclusion criteria are these studies that about formulation of soluble drugs.

Literature Review

Preparation of sennoside A and B glycoside tablet by wet granulation method according to (Leena Raju Dhoble, 2019 study)

The steps and the materials of this technique are figured in figure (2).

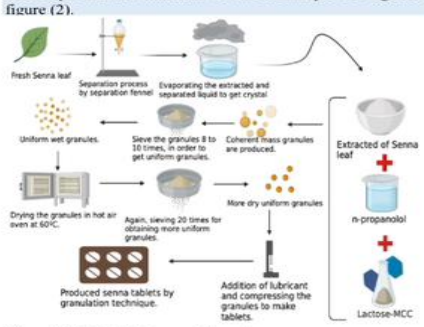

Figure (2): Wet tablet granulation steps.

Preparing oral formulation of sennoside by biogenic fabrication technique according to (Zoya Zaheer's study)

The steps and the materials of this technique are shown in figure (3).

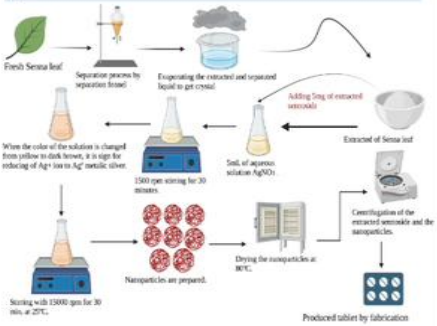

Figure (3): The steps and materials of fabrication method.

Paclitaxel nanocrystals for overcoming multidrug resistance according to (Liu et al., 2020 study)

The steps and materials that are used are shown in figure (4).

Figure (4): The steps and materials of nanocrystal preparation technique

Paclitaxel hydrogel formulation (the inhibition of tumor growth and metastasis by self-assembled nanofibers of Taxol) according to (Wang et al., 2012 study)

The materials and steps that used in this technique are showed in figure (5).

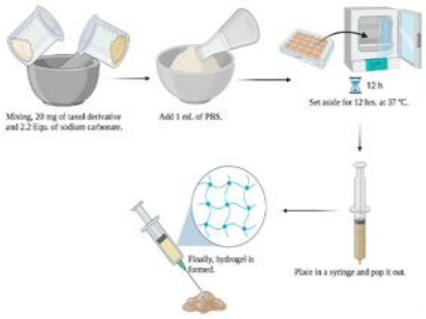

Figure (5): Hydrogel formulation technique steps and materials.

Literature Results

Result of (Leena Raju Dhoble, 2019 study):
Extraction of Senna leaves by maceration technique in 70% hydro alcoholic solvent yields the highest amount of Sennosides.

Result of (Zoya Zaheer's study):
In order to produce stable nanoparticles by fabrication technique optimum concentrations of extracted sennoside, Ag+ ions, and CTAB are requested. For instance, sennoside concentration is 120.78 mg/L, Ag+ ions concentration is 75.5 mg/L, and CTAB concentration is 921.1 mg/L.

Result of (Liu et al., 2020 study)
In terms of effect on MDR, in. experiment among other formulations being tested only PTX/TPGS could successfully inhibit MDR through inhibiting P-gp by 40%,however other formulations also inhibited proliferation effectively. Finally it was observed that amount of surfactant present and cytotoxicity are directly proportional.

Result of (Wang et al., 2012 study):
It was observed how the Taxol molecule passed gelation test through leaving it at two different temperatures both room and body temperature. Yielding57% and 95.4% subsequently. Fatal dose was roughly 7.5 times higher than that of Taxol indicating more safety.

Discussion

Extracted sennoside tablets that formulated by wet tablet granulation technique are commercially common in the markets, which are used to support bowel and digest tract health, constipation, digestion, ingestion, fever and decreasing body weight. Another novel formulation for Sennoside is fabricated sennoside tablet that used for colon cancer. But the fabricated sennoside is not available commercially, because the researches till now is not sufficient to prove for marketing of fabricated sennoside for cancer. The conventional produced paclitaxel combines with many side effects and adverse effects, we can decrease these side effects and adverse effects by the technique of formulation. Hydrogel formulation technique is the advanced technique to formulate hydrogel paclitaxel which is not available in the markets. Table (1) is compared the side effects and adverse effects of conventional and advance formulation techniques.

Table (1): Comparison between conventional techniques and advance techniques of formulation.

Conventional techniques	Side effects of conversional techniques	Advanced techniques	Side effects of advanced techniques
Wet tablet granulation for sennoside	Colon cancer, liver damage, electrolyte disturbance, worsening heart disease	Fabrication techniques	Isn't caused for colon cancer, liver damage with lesser extent
Nanoparticle technique for paclitaxel	Hair loses, numbness and risk of infection.	Hydrogel technique	Same side effect with conventional but with lesser extent.

Conclusion

In conclusion, the two various types of glycosides that we stated can be used to produce a variety of pharmacological effects, but none of these effects can be attained without formulating. The way that they are made depends on their nature and the location of their effects. For instance, sennoside is made via wet tablet granulation and fabrication, and the final product can be taken orally. And Paclitaxel which is the most famous glycoside for anticancer activities, also it can be formulate via nanoparticle technique and gel formation technique.

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