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"REVIEW ON PHARMACOKINETIC HERB DRUG INTERACTION OF LAGENARIA SICERARIA FRUIT EXTRACT AND BETA CAROTENE WITH PIOGLITAZONE"

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Abstract:It is known that the composition of phytochemicals in fruits and vegetables is beneficial to human healt h. It is also known that phytochemicals can alter the absorption properties of drugs by interacting with drug trans porter and drug
metabolizing enzyme systems, thus affecting drug pharmacology. This effect occurs mainly in the intestines and liver, where phytocheicals are abundant. Changes in the activity of cytochrome P450 and other enzymes may aff ect the fate of metabolic drugs. Plants have been used for centuries to treat many conditions, including diabetes. Many people with diabetes are known to use herbs that contain antidiabetic drugs, as well as their main treatment s, which may help cure the disease but also have the potential to be dangerous. In this review, weevaluated clinic al and experimental data on herbal
pharmaceutical interventions in the treatment of diabetes. Pharmacokinetic and pharmacodynamic interactions b etween drugs and herbs are discussed, focusing on some herbs that can be used to interact with
anti-inflammatory drugs.

Key words: **Phytochemicals, Cytochrome, diabetes, pharmacokinetic and pharmacodynamics interactions.**

I Introduction

The most common antibiotics are sulfonylureas such as tolbutamide, glibenclamide, and gliclazide; biguanide dr ugs such as
metformin, phenformin; meglitinide Naphtha drugs such as repaglinide, nateglinide, thiazolidinedione such as ro siglitazone,
pioglitazone, acarbose, glucosidase inhibitors such as dipeptidyl peptidase-4, eg sitagliptin.
Lagenaria siceraria (Cucurbitaceae) is a herb with antidiabetic properties in Ayurvedic recipes. Betacarotene, one of the active

components of Lagenaria siceraria (LS), has been reported to have anti-
inflammatory properties. There are many types of anti
inflammatory drugs combined with bloodleaf gourd, and it is the main crop in the local market.
Herbal medicine has become the first choice of patients with many diseases. Since these drugs are available direc tly from the situationand cost, their side effects are less. Patients use herbal preparations with or without their doc tor's knowledge to get better results.
Herb-drug interactions can produce many synergistic/beneficial effects as well as negative/side effects.
Many studies have been published in the past on the pharmacokinetic and pharmacodynamic interactions betwee n various medicinal plants and traditional medicines. Therefore, it is necessary to examine the interaction of medi cinal plants and their main ingredients, β-carotene, with anti-inflammatory drugs. [1,2]

1.1Plant Introduction

Lagenaria siceraria, lauki, is a bottle or dumbbell shaped plant called gourd. It belongs to the Cucurbitaceae famil y.
The round fruit is called a pumpkin. The fresh fruit has light green smooth skin and white flesh. It is widely used worldwide as food and medicine. It is a very important fruit that contains all the essential substances necessary fo r health.
The plane tree and its fruits can be eaten as vegetables. It is widely used in India. Some parts of the plant are use d to treat various
ailments such as asthma, fever, jaundice, high blood pressure, ulcers and skin problems. It is also used as a diuret ic, emetic, laxative
and sedative. It also has many therapeutic properties such as antibiotic, anti-inflammatory, anti-
inflammatory and anti-inflammatory. Many studies have revealed its antidiabetic and anticancer properties and it is also used in the treatment of many
neurological disease.

Figure 1: *Lagenaria siceraria*

1.2Taxonomic classification:

Kingdom: Plants

Family: Magnoliaceae

Class: Magnoliales

Order: Cucurbitales

Family : Cucurbitaceae

Genus: Lagenaria

Species: siceraria

1.3 Botanical description:

Lagenaria is a large herbaceous plant with stems and buds, climbing or creeping, found in wild or cultivated area s of India. Its fruit is larger, up to 1.8 m, and its leaves and stems are long.

1.4 Cultivation:

It has been grown in Asia, Europe and America for thousands of years. It is the most popular vegetable and can b e grown almost all year round. There must be warm air, humidity and sufficient humidity. Seeds can be planted when an early harvest is desired. Summer crops are planted from mid-October to mid-March.

1.5Active ingredients:

Alkaloids, phenols, tannins and known steroids. The case studies discussed below draw some conclusions. Phyto chemical

analysis.The nutritional value of the fruit is its sugar and fructose quality. Amino acids include leucine, phenylala nine,

valine tyrosine, alanine and cystine. The fruit is a good source of B vitamins, betacarotene, vitamin C and ascorbi c acid.

Bitter fruit produced Cucurbitaceae B, D, G, H, mostly Cucurbitaceae B. Cucurbitacin B is found in the leaves an d B, D

and E are found in the roots. These bitter substances are found in the fruit in the form of aglycones [3,4,5]

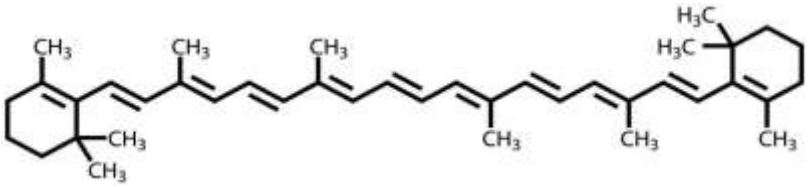

Figure 2: Structure of β carotene

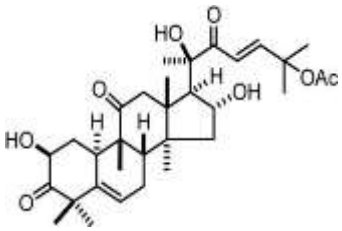

Figure 3: Curcubitacin B

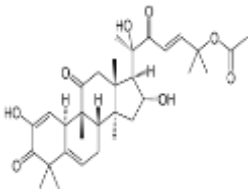

Figure 4: Curcubitacin E

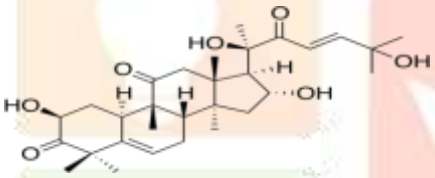

Figure 5: Structure of Curcubitacin D

1.6 Toxicity:

Cucurbitacins include cucurbitacins known to be cytotoxic. A toxic tetracyclic triterpene cucurbit compound fou nd in fruits and vegetables of the cucumber family. It is the source of the bitter taste and can cause stomach pain. In extreme cases, people have
died from drinking pumpkin juice.

Reports of consuming Lagenaria siceraria:

Between March 28, 2007 and June 23, 2010, three people, one from Delhi and two others, reported dying after dr inking the delicious
juice of Uttara. pradesh Our cases, who were over 59 years old and had diabetes (T2DM: type 2 diabetes) for the last 20 years, died
after drinking fresh fruit juice or fruit juice and fruit mixture. According to patient information, the juice is very bitter.
26 people who complained of stomach pain and vomiting after drinking fresh fruit juice applied to various hospit als in the country.

Abdominal pain and hematemesis were observed in 18 (69.2%) and 19 (73.1%) patients, respectively. Biochemic al studies show high enzyme levels. More than 50% of patients complain of hypotension. Endoscopic findings us ually show large blood clots in the
esophagus, stomach, and duodenum. Bottle gourds contain toxic tetracyclic triterpenoids called cucurbitacin, whi ch are responsible
for the bitter taste. There is currently no antidote for this poison and doctors treat these conditions [6].
Advise the public and doctors on the use of pumpkin

The public should understand and follow the following steps:

Sugar juice should not be small and should be tasted.
Luffa juice should not be mixed with other fruit juices.
If the patient feels discomfort (nausea, vomiting, diarrhea), drink immediately and go to the nearest hospital.

For doctors:
Patients with symptoms (discomfort, nausea, vomiting, diarrhea, gastrointestinal bleeding after drinking the juice) should
immediately consult a doctor and receive careful treatment and pain management such as intravenous fluids/cryst alloids/blood
products/freezing. Plasma to maintain hemodynamic and electrolyte balance;
Insert Lyell tube for colonization and assess for gastrointestinal (GI) bleeding - collect aspirate;
Proton pump inhibitors should be given to treat gastrointestinal bleeding and other complications. appropriate tre atment [6].

II Drug Overview

2.1.1 Chemical: β-carotene

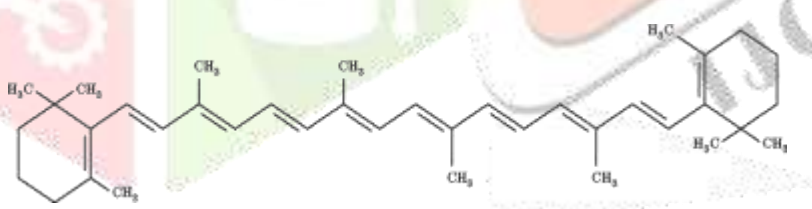

Figure 6: Structure of β-carotene

2.1.2 Structural formula:

Table 1: Chemical description of β-carotene

IUPAC names	1,3, 3 - Trimethyl 2-[3,7,12,16-tetramethyl-18-(2,6,6-trimethylcyclohexan-1-en-1-yl)sectadecan-1,3,5,7,9,11,13,15, 17-nonaen- 1-yl]cyclohex-1-ene
Experimental formula	C40H56
Molecular weight 536.9 g/mol	Molecular weight 536.9 g/mol
CAS NO	49763-96-4
Boiling point and melting point	654.7°C 183°C
Storage condition	against light and moisture
Solubility	Insoluble in water.

2.1.3Pharmacological effects:

Hyperglycemic activity:

Studies on the effects of low dose and high dose β-carotene on ischemia/reperfusion myocardial experiments in non-diabetic rats showed that low dose (LD) of sugar improved BC. . During ischemia, cardiac function, IS decreased , and tissue antioxidant capacity increased, and these effects were eliminated when the amount of BC was controlled. Additionally, high-dose (HD) β-carotene treatment increased HO-1 expression. There is also evidence that HO-1 may play an important role in diabetes and glucose metabolism. In addition, the fact that both beta-carotene and gamma-tocopherol interact with the same gene and affect the risk of diabetes, albeit in opposite directions, shows that the protein encoded by this gene (SLC30A4) may play an important role in the disease.

In fact, this protein is abundant in the insulin-producing cells of the pancreas and helps transport zinc into the cells. This leads to the release of insulin, which i s adequately released by the pancreas and well absorbed by the muscles, liver and fatty tissue, which can prevent the danger of sugar in the blood and limit the development of type 2 diabetes in the long term. Diabetes [7,8].

2.2.1Drug: Pioglitazone

2.2.2 Structural formula:

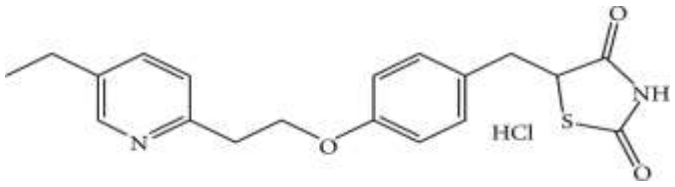

Figure 7: Structure of pioglitazone

Table 2: Chemical profile of pioglitazone

IUPAC name	(RS)) -5-(4-[2-(5-ethylpyridine-2-yl)ethoxy]benzyl)thiazolidine-2,4-dione
Experimental formula	C19H21ClN2O3S
Molecular weight	392 .9 g/mol
CAS No.	111025-46-8
Appearance	White crystalline powder
Melting point	193-194°C
Storage condition	Store at room temperature
Solubility	DMSO: ≥10 mg/mL

2.2.3Description:

Pioglitazone hydrochloride is an oral hypoglycemic drug that works by lowering insulin concentration. Pioglitaz one
thiazolidinedione monohydrochloride belongs to a different class of drugs and has different effects than sulfonyl ureas, metformin, or
alphaglucosidase inhibitors. It can be used as monotherapy or in combination with a sulphonylurea or insulin in t he treatment of type 2 diabetes (non-insulin-
dependent diabetes, NIDDM). Pharmacological studies have shown that pioglitazone increases the sensitivity of muscle and fatty
tissue to insulin and inhibits hepatic gluconeogenesis. Pioglitazone improves blood sugar control while lowering insulin levels.
It is a peroxisome proliferator-activated receptor-
gamma (PPARγ) agonist that causes reversal of insulin resistance and thus increases insulin sensitivity. It is used in the treatment of
type 2 diabetes. It increases the sensitivity of muscle and fat to insulin, inhibits hepatic gluconeogenesis, and ma y improve glycemic
control while lowering insulin.

2.2.4Mechanism of Action:
The mechanism of action depends on the presence of insulin and its decrease. Peripheral and hepatic insulin resis tance causes strong
insulin dependent glucose release, thereby repairing and reducing glucose in the liver.
Pioglitazone is a potent, highly selective peroxisome proliferator-activated receptor-γ (PPARγ) agonist.

PPAR receptors are found in tissues important for insulin action, such as adipose tissue, skeletal muscle, and live r. Activation of
PPARγ nuclear receptors regulates the transcription of several insulin-
regulated genes involved in the regulation of glucose and lipid metabolism. In animal models of diabetes, pioglit azone reduces the
hyperglycemia, hyperinsulinemia, and hypertriglyceridemia that are characteristic of insulin resistance such as t ype 2 diabetes,
the recruitment of insulindependent tissues, and has been observed in various animal models of insulin resistance .
Because pioglitazone potentiates the effects of insulin (by reducing insulin secretion), it does not reduce blood gl ucose in animal
models lacking endogenous insulin [8].
2.2.5Absorption: After oral administration, pioglitazone first enters the body in the fasting state and can be dete cted in the blood for 30 minutes to 2 hours. Food slows the time to peak blood pressure by 3 to 4 hours but does not change absorption.
2.2.6
Distribution: The meanapparent volume of distribution (Vd/F) of pioglitazone after a single dose is 0.63 ± 0.41 (mean ± SD)
L/kg body weight. Pioglitazone is highly (>99%) protein bound in human serum, primarily to serum albumin. Pi oglitazone also binds to other proteins in the blood
but with low affinity. Metabolites M-III and M-IV also bind to serum albumin (>98%).
2.2.7Metabolism: Pioglitazone is metabolized mainly through hydroxylation and oxidation; Metabolites are also partially converted
to glucuronic acid or sulfate conjugates. Metabolites M-II and M-
IV (hydroxyl derivatives of pioglitazone) and M
III (keto derivatives of pioglitazone) are drugs used in animal models of type 2 diabetes.
Except pioglitazone, MIII and MIV are the main types of drugs in human diabetes. In vitro data indicate that mor e than one CYP
isoform is involved in the metabolism of pioglitazone. The relevant cytochrome P450 isoforms are CYP2C8 and to a lesser extent
CYP3A4, but there are many other isoforms, including mostly extrahepatic CYP1A1 [8].
2.2.8Clearance and elimination: Approximately15% to 30% of pioglitazone is found in urine. Renal clearance of pioglitazone is
negligible and the drug is excreted mostly as metabolites and conjugates. It is estimated that most of the oral dose is eliminated
unchanged or as metabolites via bile and feces within 16 to 24 hours. Washing: 5 to 7 litres/hour.
2.2.9Dosage: Initially 15-
30 mg per day with food; The dose can be increased from 15 mg to 45 mg daily with careful monitoring.
Side effects: muscle pain, sore throat, broken bones, increased cholesterol, blood cancer, visual impairment/blind ness, shortness of
breath, weight gain, blood in the urine, and stomach pain.

2.2.10Drug interactions: aminosalicylic acid, amlodipine, amodiaquine, atenolol, atorvastatin, darunavir, dapsone, dexamethasone,
fluconazole. Haloperidone, griseofulvin. Pharmacodynamic and therapeutic effects: Clinical studies have shown that pioglitazone can increase insulin sensitivity in patients with insulin resistance. It increases the sensitivity of cells to insulin, increases insulin-
dependent glucose production, increases liver insulin sensitivity and improves glucose homeostasis. In patients with type 2 diabetes,
pioglitazone reduces insulin resistance, causing blood sugar, plasma insulin levels and A1C values to decrease. According to the results of the openlabel study, the reduction in blood sugar levels of pioglitazone occurred over at least one year. In
controlled studies, the use of pioglitazone in combination with sulfonylureas has been shown to have an additive effect on glycemic
control. Patients with lipid abnormalities were enrolled in a placebo-
controlled study of pioglitazone monotherapy. Overall, patients receiving pioglitazone experienced a decrease in triglycerides and
a moderate increase in lipoprotein cholesterol, whereas changes in lowdensity lipoprotein and total cholesterol did not correlate with patients receiving pioglitazone,placebo group.
Similar results were observed in 16- and 24-week clinical studies with pioglitazone and sulfonylureas [9].

III Plant-Drug Interactions

Diabetes is a global disease that causes inadequate or inadequate secretion of insulin. The incredible problem of producing insulin is along
term problem for people with diabetes that has no effective treatment. Although significant advances have been made in the use
of synthetic drugs to treat diabetes, scientists are still working to find new plants that can act as anti-diabetic drugs.
There are two types of diabetes: type 1 (T1DM) and type 2 (T2DM) diabetes. T1DM, also known as insulin-dependent diabetes (IDDM), is caused by insufficient insulin production.
However, T2DM is often associated with the body's inability to respond to insulin (insulin resistance) and is therefore called
non-
insulindependent diabetes (NIDDM). These herbal remedies are considered safer and less toxic than synthetic drugs.
Many medications are available to treat the disease, but there are issues regarding their affordability, effectiveness and side effects
(Christhudas et al., 2013). Although many medications help control diabetes, they often do not cure the disease. Herbs and
supplements are safer. Medicines based on natural products are used as hypoglycemic drugs to reduce complications and side effects
(Loizzo et al., 2008).
In the treatment of type II diabetes, inhibition of the digestive enzymes alpha-amylase and
alphaglucosidase provides a strategy to prevent carbohydrate hydrolysis and block glucose in the body.
These enzymes are from the hydrolase family and hydrolyze polysaccharides into glucose, which then enters the blood.
Diabetics can control blood sugar after a meal by preventing carbohydrates from mixing into the blood. Acarbose is an N-

glycosylated triglyceride that is a good inhibitor of carbohydrate digestive enzymes, but has side effects such as c onstipation, upset
stomach, and diarrhea (Wang et al., 2010). The production of free radicals in the human body can cause diabetes. Antioxidant and
antidiabetic activities are interrelated.
The liver metabolic enzyme system, particularly the cytochrome P450 (CYP450) isoenzyme family, is also a me chanism for the
pharmacokinetics of HDIs. Many antidiabetic drugs are receptors for CYP450 isoenzymes; for example, CYP2C 8 is pioglitazone,
repaglinide, and rosiglitazone, and CYP2C9 is glibenclamide, glimepiride, glipizide, napaglide Nel, and rosiglita zone, and CYP2C9 is glibenclamide. Many herbs are also thought to affect the CYP450 system. For example, St. St. John's wort inhibits CYP2C and
CYP3A, and ginkgo inhibits CYP3A4, CYP2C9, and CYP2C19.

3.1 Pharmacodynamics

HDIs can alter the effects of drugs/herbs through their effects on various organs, receptor sites or enzymes. This debate can lead to
hatred, alliances, alliances. For example, many plants have antioxidant properties that may help reduce oxidative stress that causes
diabetes. Some drugs that are effective in lowering blood sugar, such as 3-hydroxy-3-methylglutaryl
CoA reductase inhibitors, have also been shown to have antioxidant activity. When herbs and drugs are used toge ther,
pharmacodynamic HDI (additive/synergistic) may occur induction.
In addition to inhibition of intestinal and hepatic metabolic enzymes such as CYP enzyme family enzymes and tr ansporters. and
efflux proteins (Meijerman et al. 2006; Yoo et al. 2007; Nowack 2008; Yoo et al. 2008). In particular, preactivati on of CYP enzymes often affects the oral bioavailability of drugs, so the combination of herbal products with CY P function has been shown to cause
changes in the blood of the affected drug. It is a family of monooxygenases found mainly in intestinal and liver c ells and can catalyze
many phase I metabolic reactions, such as oxidation, hydroxylation, S- and O
demethylation, and oxidative deamination of more than 70% of drugs. is responsibility (Karyekar et al., 2017). 2 002). The CYP
superfamily is involved in the biotransformation of many exogenous and endogenous compounds (Hiratsuka 201 2; Nebert and Russell 2002).
CYP enzymes belonging to families 1, 2 and 3 are mainly involved in the metabolism of exogenous drugs, while other enzymes play
important roles in the production and elimination of endogenous drugs such as hormones, bile acids and fatty aci ds. These herbs can
bind to medications and prevent their absorption, thus reducing the amount used in the body.
Replacing the protein with other chemicals will increase the potency of the drug. Although protein changes have been identified as
potential drug interactions, there are no reports of drug
drug interactions resulting from changes in the drug via protein binding sites
(Wang and Chou 2010). Modifying renal clearance is an alternative to herbdrug interactions, where herbal produ cts that have the

potential to interfere with renal function may alter renal clearance. Changes in renal function may result from in hibition of tubular secretion, tubular reabsorption, or glomerular filtration (Isnard Bagnis et al., 2017)Herbal prod ucts taken as diuretics often alter renal
function, but herbal diuretic mechanisms are complex and inconsistent. Some herbs increase glomerular filtration rate without
stimulating electrolyte secretion, while others directly stimulate renal tubules (Al-
Ali et al., 2003; Crosby et al., 2001).
Therefore, herbs that can interfere with the renal clearance of the drug should be considered as having the potenti al to create
pharmacokinetic herb-drug interactions.

3.1.1Plant

drug interactions at the absorption level: Effects of the plant on efflux transporters: The effect of drug efflux o n
concentration gradients is mediated by ATPbinding (ABC) transporters, which in turn are mostly found in intesti nal epithelial cells.
Membranes and endothelial cells of microvessels in the human heart, kidney or brain. ABC post can be easily cu stomized with
products such as medicines, herbs, food and beverages. Induction and inhibition of fluid transporters by herbs ca n lead to therapeutic
failure and toxiclevels. P-glycoprotein (P-gp): P-gp is known as multidrug resistance protein or ABC subfamily.
Modification of Pgp by herbal components can directly interact with one or more binding sites of the Pgp molecu le, either
competitively or non
competitively or through stimulation of drug efflux. Phytochemicals can affect ATP binding, hydrolysis, or the binding of ATP-hydrolyzing molecules, thus depleting the energy that drives the translocation of P-
gpbound substrates.
Interactions of Herbs in Gastrointestinal Disorders: Herbs can cause diarrhea, shorten the time the drug stays in t he intestine, and
reduce the contact time with the epithelium, causing the drug to not fit into the body.

3.1.2Interaction between plants and drugs at the level of distribution:

Changes in binding to plasma proteins (only the free part of the drug in plasma is the drug and changes in bindin g to plasma proteins may lead to increased exposure) distribution (of the drug) may be affected, leading to increa sed drug use or adverse effects related to
the decline of synthetic drugs may be reported.

3.1.3Herb-Drug Interactions at the Metabolic Level:

Pharmacokinetic herb-drug interactions occur when drug
metabolizing enzymes are induced or inhibited by mixing herbs
For example, induction of CYP enzymes often leads to therapeutic failure due to insufficient plasma concentratio n of the drug.
This interaction is carried out by the cytochrome P450 (CYP) metabolic enzyme family (Phase I enzymes) and n on-
CYP enzyme systems (Phase II enzymes). Important CYP subfamilies responsible for drug metabolism are 1A1, 1A2, 1A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4, and 3A5 (Ono et al., 1996). Phase II enzymes, including uridine dip hosphate glucuronosyltransferase (UGT), Nacetyltransferase (NAT), glutathione transferase (GST), and sulfotran

sferase (ST), aid in the removal, catalytic polarity, and binding of ionizable groups to phase I metabolites. Induction of metabolic enzymes is a slow process that stimulates the activation of genes and increases the genes or proteins of the affected enzymes. Inhibition of metabolic enzymes occurs when herbs can reduce the expression or activity of metabolic enzymes in a competitive or noncompetitive manner. Induction of CYP enzymes can lead to low plasma levels and therapeutic failure, whereas inhibition of CYP enzymes can lead to high plasma levels and increased toxicity.

3.1.4Plant-Drug Interactions in the Elimination Phase:

The main purpose of drug elimination is through the kidneys and bile, but bile elimination does not provide herbal-drug interaction. Drugs excreted by the kidney may participate in drug interactions through a variety of mechanisms, including competition for transport, changes in glomerular filtration, and passive tubular reabsorption. Most drugs excreted by the kidneys are involved in the interaction of herbs through competition for transporters or through different mechanisms such as glomerular filtration, passive tubular reabsorption or active secretion and transfer in urinary pH (Isard et al., 2004). The mechanism of vegetative diuresis is complex and inconsistent. Some herbs can increase glomerular filtration rate without stimulating electrolyte secretion, while others can directly stimulate renal tubules (Crosby et al., 2001) [9].

3.1.5Pharmacodynamics Plant-Drug Interactions:

Pharmacodynamics refers to the relationship between the concentration of a drug at the site of action and its effect, as well as the relationship between the use and side effects of the drug and time. Effects. The effect of the drug on the site of action depends on the binding of the drug to the receptor. These receptors are found on neurons in the central nervous system (like opiate receptors) and can affect pain; in the heart muscle, where they can affect contraction; and even in bacteria, they can affect the persistence of the organism in its cells. wall. These interactions may occur when herbal products are used as supplements, combinations, or as anti-medication activities. Pharmacodynamic interactions involve the pharmacological properties of interacting drugs and may affect the body, receptor sites, or enzymes. It affects the effects of drugs by increasing or changing their effects.

Pharmacodynamic interactions are interactions between drugs that cause changes in the response to the drug (for example, changes in the body and the mechanism of action of the drug in the body, and the relationship between changes in drug concentration and drug. concentration). Pharmacodynamic interactions may lead to enhancement or inhibition of the pharmacological effects of the compoundTherefore, herb drug pharmacodynamic interactions may involve changes in the pharmacological effects of drugs through additive, synergistic, or antagonistic effects.

3.1.6Antagonism:

Herbs may interfere with the desired effect of the combined drug, thus reducing the pharmacological effect of the drug effects of drugs (Scott and Elmer 2002; Williamson et al. 2013). Ephedra or caffeinated herbs (kola nut, guarana, yerba mate, green tea) are often used with many weight loss products to produce additive cardiovascular effects that antagonize the effects of antihypertensive medications.

3.1.7Additional effects:

Herbs can produce effects similar to drugs and therefore increase these effects when taken together (Kang and Pa rk 2010; Scott and
Elmer 2002; Williamson et al. 2013). Therefore, Chinese herbal tranquilizers, anticoagulants, antihypertensives a nd other medications may also increase the effect of the drug. For example, Agrimony extract produces an additi ve hypoglycemic effect when taken with
antiinflammatory drugs (Gray and Flatt 1998; Swanston et al. 1990). Although valerian strengthens the hypnotic activity of
benzodiazepines, ginkgo, garlic and ginger also strengthen the anticoagulant effect of warfarin (Kuhn 2002; Scott and Elmer 2002;
Fetrow et al. 1999).

3.1.8Synergy

The relationship of the plant with the drug will affect the effectiveness of the drug. For example, some natural tre atments

Ø will increase the side effects of the drug and possibly cause toxicity.

Ø Reduce the use of medications that will cause treatment failure.

Ø Drugs that change the effect of the drug cause unexpected problems.

Ø It may increase the therapeutic effect of the drug and cause overdose. [11,12,13]

IV The role of cytochrome P450 enzymes in drug interactions:

CYP450 enzymes are the main catalysts involved in drug metabolism. CYP450 is a heme protein superfamily co ntaining 57 genes
responsible for oxidative metabolism and metabolism of most xenobiotics (drugs, foods, and pollutants) and end ogenous receptors
(such as steroids, cholesterol, and bile acids). Impairment of CYP
mediated drug metabolism during concurrent administration of
other drugs or exposure to certain exogenous drugs is considered the most common cause of drug interactions. T he first number in
CYP terminology. CYP represents families, letters represent families
and numbers represent them. The following subfamilies
represent different enzymes and polypeptides of this subfamily. Although there are at least 18 different CYP450 i soenzymes in the
human liver, only 10 isoforms in families 1, 2, and 3 (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C 19), CYP1, CYP2C. Most drugs are produced in the liver. P450 enzymes in animals differ from humans. Howev er, some specific CYP isoforms also have similarities [13,14].

Table 3 : Some CYP enzymes in man, mouse, rat, dog and monkey.

Family	Subfamily	Human	Mouse	Rat	Dog	Monkey
CYP1	A	1A1, 1A2	1A1, 1A2	1A1, 1A2	1A1, 1A2	1A1, 1A2
	B	1B1	1B1	1B1	1B1	1B1
CYP2	A	2A6 2A7 2A13	2A4 2A5 2A12 2A22	2A1 2A2 2A3	2A13 2A25	2A23 2A24
	B	2B6 2B7	2B9 2B10	2B1 2B2 2B3	2B11	2B17
	C	2C8 2C9 2C18 2C19	2C29 2C37 2C38 2C39 2C40 2C44 2C50 2C54 2C55	2C6 2C7* 2C11* 2C12* 2C13* 2C22 2C23	2C21 2C41	2C20 2C43
	D	2D6 2D7 2D8	2D9 2D10 2D11 2D12 2D13 2D22 2D26 2D34 2D40	2D1 2D2 2D3 2D4,2 D5 2D18	2D15	2D17** 2D19** 2D29** 2D30** 2D42**
	E	2E1	2E1	2E1	2E1	2E1
3	A	3A4 3A5 3A7 3A43	3A11 3A13 3A25 3A41 3A44	3A1/3 A23 3A2* 3A9* 3A18 * 3A62	3A12 3A26	3A8

**Special methods

*Gender differences

In the preclinical development of new drugs, animal models are used to predict the metabolic behavior of new co mpounds in humans. In the first stage of drug development, interactions with plants are used to prevent or reduce the effects of toxic substances on plants.

It is important to use appropriate in vitro and in vivo models to identify agents that can enter drugs. However, hu mans differ from animals in isomeric composition, activity, and catalytic activity of drug metabolizing enzymes.

Specific isoforms of CYP1A, CYP2C, CYP2D, and CYP3A exhibit significant differences in catalytic activity. This should be taken into account when extrapolating metabolic data from animal models to humans. Selecting a nd finding the best animals to model human drug metabolism remains a difficult problem in drug development. Materials used in me tabolism studies should be able to be correlated with toxicity endpoints. Using human CYP proteins and expression lines is not th e correct method.

The species most commonly used in metabolic studies are mice, rats, rabbits, dogs and monkeys, followed by gui nea pigs and hamsters. Compared to humans, the CYP profile is imperfect (Martignoni et al., 2006). Plant prod ucts/nutrients can be metabolized by CYP and released into non-toxic metabolites, but toxic metabolites may be produced.

The mechanisms of phytotoxicity are still unclear, but increasing knowledge suggests that important plants are in volved in phytotoxicity and carcinogenesis through bioactivation to produce reactive metabolites/intermediates. It is hypot hesized that reactive metabolites formed after bioactivation of herbal drugs bind covalently to cellular proteins an d DNA, causing toxicity through various factors such as direct cytotoxicity, oncogene activation, and hypersensit ivity reactions. Xenobiotics, drugs, and many naturally occurring foods or herbs can interact with the CYP450 system in various ways (Lehmann, 1998), thereby altering drug clearance and effectiveness (Rendic, 2002).

• A compound may be a substrate for one compound or for more than one CYP isoform. If the first isomer is satu rated, it will become the substrate of the enzyme.

• Drugs can act as inducers of CYP isoforms, substrates of CYP isoforms, or act on multiple enzymes simultaneo usly. The induction process increases the metabolic rate of this enzyme substrate. Drugs may also be inhibitors of CYP450 enzymes. There are several mechanisms of inhibition, and a compound may inhibit several isoforms including others than those for which it is a substrate (Zhou, 2003). On the other hand, if the substrate is a prodrug activated by CYP mediated metabolism, inhibition of its metabolism can reduce its effects and induction can either enhance or reduce its effects and toxicity, depending on the effects of induction on the further metabolism or excretion of the active metabolite.

4.1Mechanisms of CYP450 inhibition:

Drug metabolism could be inhibited by different mechanisms including:

(i) reversible enzyme inhibition,
(ii) reduction of enzyme available for metabolism by irreversible inhibition or suppression of its synthesis
(iii) reduction in the supply of enzyme cofactor(s).
(iv) Inhibition of drug metabolism could result in an increase in drug plasma concentration (which may result in drug toxicity) and a decrease in the concentration of its metabolites, which could be clinically significant in cases of active or toxic m etabolites.

Mechanisms of CYP450 induction:

4.2 Drug metabolism could be enhanced by different mechanisms including:
(i) an increase in the amount of enzyme available for metabolism (induction), which could be achieved by transcr iptional activation, mRNA or protein stabilization
(ii) an activation of enzyme metabolic activity, which is different from induction in that the amount of the enzym e available for
metabolism is not altered but its catalytic activity is stimulated in the presence of the activator
(iii) an increase in the supply of enzyme cofactor when it is the rate limiting step of metabolism. Induction may i ncrease the amount
of P450 present and enhance the speed of oxidation and clearance of a drug. The time course of enzyme inductio n is difficult to predict because many factors, such as drug half-
life and enzyme turnover, determine the induction time. The induction time depends on the time required for enz yme degradation and new enzyme formation. [13,14]

V Carrot:
Carrots are one of the most popular root vegetables throughout the world, including the United States, and are the most
important source of dietary carotenoids. . The inside is considered food. Various foods. Many researchers have in vestigated substance
in carrots including β
carotene and panaxitol (Surles et al., 2004 ; Sikora et al., 2009 ; Sun et al., 2009). The presence of many antioxidant carotenoids, especially betacarotene, may be responsible for the biological and chemical properties of carrots. PST activity(Yeh and Yen 2005)and CYP1A2 activity decreases (Harris and Jeffery 2008). Bradfield an d carrots inspired others to report that
carrots increased ethoxycoumarin Odeethylase (ECD) activity in rat models (Bradfield et al., 1985). Interactions between herbs and
antibiotics often
cause blood sugar to rise or fall, affecting glycemic control. Antidiabetic drugs have been shown to potentially interact with herbal products, including the CYP2C8 substrates pioglitazone, repaglinide and rosiglitazone; CYP 2C9 substrates are
glyburide, glimepirideglipizide, glibenclamide, and rosiglitazone; CYP2C9 substrates are glyburide, glimepiride, glipizide,
glibenclamide and rosiglitazone; rosiglitazone rules and repaglinide. [16].

VI. Herb-drug interactions:

6.1Pioglitazone-Aloe vera:
The main components include carbohydrates (galactoserich polysaccharides) and galacturonic acid.
This herb has many medicinal use
including beauty, immunity and body care. Aloe vera treatment has been shown to lower blood
sugar and blood pressure and improve lipid profile in diabetic patients (Choudhary et al., 2014). Due to its hypog lycemic properties,
aloe vera interacts with anti
inflammatory drugs. Aloe vera might lower blood sugar. Many studies have shown the effects of
aloe vera and anti-inflammatory drugs. Glibenclamide and sulfonylureas exert anti-
inflammatory effects by inhibiting ATP
sensitive K+ channels in pancreatic β cells, causing cell membrane depolarization and subsequent insulin release . The combination ofaloe vera and anti-
inflammatory drugs often causes additional side effects. Aloe tends to produce a stronger anti
hyperglycemic effect than glyburide, pioglitazone and repaglinide alone.

6.1.1Importance and Application: Aloe vera can be used to promote healthy diabetes, and some oral aloe vera preparations have been shown to be effective in treating hypoglycemia. In fact, aloe vera has traditionally been u sed to treat diabetes. Therefore, if a patient taking anti-
diabetic medication wants to try oral aloe vera, it would be a good idea to raise blood sugar more frequently [16, 17]

Figure 8: Aloe vera

6.2Pioglitazone - Cassia Seed:

Cassia Seed and Cassia Seed plant are used in the treatment of diabetes in Indian and traditional Chinese medicin e. While the
flavonoid content of cassia seeds has anti
hyperglycemic properties, the polyphenol content of cassia seeds has antioxidant
properties. Cassia fistula hexane extract (0.45g/kg) was found to have similar effects as glyburide when administ ered to STZ-treated rats. Similarly, cassia showed anti-hyperglycemic effects in normal and alloxan induced rats. Cassia inhibits CYP2C9 enzyme activity and its substrates are glyburide, glimepiride, nateglinide and rosiglitazo ne.
The substrates of the CYP3A4 enzyme are pioglitazone and repaglinide, indicating that this plant has anti inflammatory properties and may contain additives. Singh and Bharadwaj studied the hypoglycemic activity of th e wild plant Cassia
and found that it had significant hypoglycemic activity in normal albino rats but no significant hypoglycemic effe ct in alloxan-
induced diabetic albino rats (Singh and Bharadwaj 1975). Nirmala et al. (2008) reported the hypoglycemic and c holesterol-lowering effects of Cassia dry bark hexane extract on normal and streptozotocin
induced diabetic rats and found that 0.45 g/kg of the
extract was equivalent to glyburide. Take drugs. The antioxidant and polyphenol content in the extract may contr ibute to its anti-hyperglycemic and antilipidemic effects (Nirma-la et al., 2017; 2008).
In normoglycemic and streptozotocininduced diabetic rats, acute and chronic oral administration of senna seed h usk aqueous extract
rapidly reduced blood glucose and resulted in significant improvement in oral glucose tolerance tests (Ratnasoor iya et al., 2017;2004)Cassia seeds have significant anti-hyperglycemic effects on normal and alloxan-
induced diabetic rats. The anti
inflammatory properties of Cassia seeds may be due to the presence of flavonoids (Malpani et al., 2017; 2010).

6.2.1Importance and use:

Animal studies have shown that Cassia vulgaris and Cassia vulgaris extract have anti-hyperglycemic properties, and these results confirm the ethnomedical use of the plant in the treatment of T2DM (Ali et al., 2012)

Since cassia and cassia seeds have anti-diabetic properties, they should be used with caution and care when combined with anti-diabetic medications. Additionally, simultaneous use of Cassia seeds with CYP substrate hypoglycemic drugs ma y lead to drug interactions [17,18].

Figure 9: Cassia

6.3Karela- Glibenclamide

Karela is often called bitter melon because of its taste. Its juice contains many chemical compounds, including st erols, glycoside compounds and mogroside peptides. Karela is a medicinal plant that has been extensively studied in the treatment of diabetes. Karela (bitter melon) enhances the hypoglycemic effect of antidiabetic drugs (Williamson et al., 2013). Due to its hypog lycemic effects, Karela may interact with antidiabetic medications. Karela can produce insulinlike effects and stimulate insulin p roduction (Raman and Lau 1996), thus antiinflammatory drugs have additive effects. The effects of metformin, glyceramide, and gl yburide are said to increase with use. In a clinical trial, diabetic patients were given 400 mg of chloroform/bencar ella extract containing 50% of the total dose of metformin or glibenclamide. The results showed that the combine d intervention was better than metformin or carbamine alone; This indicates the possibility of additive effects. Th e same results were obtained in animal studies; Carrera juice/extract and metformin treatment showed better results than treatment alone in a diabetic rat model.

6.3.1Importance and management:

The hypoglycemic activity of karrela appears to be well established, but the best clinical studies on karrela have yielded limited result. Aqueous extract powder of Karela (an edible vegetable) appears to be a safe alternative to hypoglycemic drugs in diabetic patients (Virdi et al., 2003). Therefore, doctors need to know that patients can use Karela together with medications used to control diabetes (Jellin et al., 2014; Williamson et al., 2014). 2013) [17,18]

Figure 10: Karela

6.4Gymnema - Metformin

Gymnema is native to southern India and its medicinal properties come mainly from triterpene saponins. Gymnema sylvestre is used medically to treat diabetes, rheumatism and cough. Gymnemic acid is a pentacyclic triterpenoid and the main plant extract of
Gymnema gymnatum with antiinflammatory properties. This plant has been used to treat diabetes for nearly two thousand years. The
interaction of Gymnema cambogia (100 and 500 mg/kg orally) with metformin (50 and 100 mg/kg) was studied in STZ-
induced diabetic rats. This treatment has been shown to reduce metformin bioavailability and blood sugar levels; However, although
histopathological examination showed an increase in islet cell volume after treatment, blood sugar was not higher than metformin
itself. In animal studies using rat models of antiinflammatory drugs, metformin plasma levels decreased and blood glucose levels
increased in animals treated with the combination of gymnema gymneifolia leaf tea and metformin, compared with control animals
receiving metformin alone. It occurs in metformin and gymnema. A similar study in diabetic rats showed that the bioavailability of
metformin was reduced across doses. However, the combination lowered blood sugar more than metformin or gymnema alone. These findings suggest that more research is needed on diabetic patients to determine the effects of gymnema tea and metformin together on diabetes. Glibenclamide interferes with the regulation of glucose in body tissues through ATP-sensitive potassium channels and no Hyperglycemia-induced mediated vasodilation. Glyburide interferes with mitochondrial bioenergetics in non
pancreatic cells through changes in membrane ion permeability.
Insulin-
independent glucose transport by the GLUT1 protein appears to be one of the additional mechanisms of the immune system.
Glibenclamide has been reported to increase the total content and plasma membrane level of GLUT1 in L6 myotubes. Chronic
administration of sulfonylureas to cultured cardiomyocytes has been shown to double blood glucose levels via an insulin-
independent pathway. This may affect the expression of GLUT1 protein. Gymnemic acid works differently in the body in diabetics by reducing blood sugar and insulin levels and blocking the intestinal absorption of glucose. In recent years, the incidence of diabetes
has increased all over the world and herbal products have become increasingly popular in the international market (17,18).

Figure 11: Gymnema

VII.Report Lagenaria siceraria Herbal Interactions:

Interaction between Lagenaria siceraria ethanol extract and glyburide in diabetic rats. (Deshpande J.R et al.; 2008)

The purpose of this study is to investigate the medical use of Lagenaria siceraria fruit extract and glibenclamide. Alloxan
monohydrate (150 mg/kg, one intraperitoneal dose) causes hyperglycemia in rats. Rats that developed hyperglyc emia (blood sugar
above 260 mg/dl) 48 hours after alloxan administration were divided into 5 groups, with 6 rats in each group. Group 1 is normal control. Group 2 is hyperglycemia management.
Groups 3 and 4 had hyperglycemia and received EELS (100 and 200 mg/kg orally) for 14 days.
Group 5 received glyburide (5 mg/kg orally) for 14 days. Plasma glucose concentrations were evaluated on days 0.7 and 14 of
treatment, and the percentage reduction in glyburide was 57.8% and 64.3% on days 7 and 7, respectively. Accord ing to the 14th.
Alloxan increases blood lipid levels of total fat (TC), triglycerides (TGL), low-density lipoprotein (LDL-
C), and low-density lipoprotein cholesterol (VLDL-C) and reduces low-density lipoprotein cholesterol (HDL). -
C) level. These changes were prevented by the use of ethanolic extract of Lagenaria siceraria (EELS) (100 and 2 00 mg/kg).
Therefore, adding EELS can effectively control blood sugar and prevent low blood sugar; It can improve lipid m etabolism, prevent
development of atherosclerosis, improve the antioxidant effect in experimental diabetic mice, and prevent diabet es, lipid
peroxidation. [19]

7.1Interaction of methanolic extract of Lagenaria siceraria with glyburide in diabetic rats. (Perona Saha et al.; 2011)

This study aimed to determine the interaction of glyburide with the methanol extract of Lagenaria siceraria extrac t. Streptozotocin (50 mg/kg, intraperitoneally) causes hyperglycemia in rats. Methanol extract of Lagenaria sicera ria was made at doses of 200 and 400 mg/kg (oral). 14 days. Glibenclamide (500 µg/kg) was used as control drug . Wistar albino rats were divided into 5 groups, with 6 rats in each group. The treatment period is 14 days. Group I: mice received vehicle only from start to finish; Groups II, III, IV and V: STZ-
induced diabetic rats. The Group II streptozotocin control group received vehicle only. While 200 mg/kg and 400 mg/kg body weight of Purple Cucurbita methanol extract were administered orally to Groups III and IV, respecti

vely, glyburide (0.5 mg/kg, orally) was administered to Group 5. STZ
induced hyperglycemia is an effective treatment. Trial designed to examine prevention of
hyperglycemia. Due to its properties, STZ penetrates the low GLUT2 transporter of the plasma and selectively en ters the β cells in theislets of Langerhans, causing the destruction of β cells, resulting in decreased insulin secreti on and subsequent increase in insulin
secretion. . reduced. High blood sugar is called hyperglycemia. Decreased blood sugar may be due to increased withdrawal or
peripheral glucose consumption. However, studies on euglycemia have shown that MELS has no effect on eugly cemia. This means
that the extract may act through other pancreatic processes, not stimulating β
cell insulin secretion and causing an anti hyperglycemic
effect rather than a hypoglycemic effect, i.e. not affecting euglycemia as unnecessary drugs should. The followin g may help. The total phenolic and flavonoid content in the extract was determined to establish a relationship bet ween medicinal properties and anti-
inflammatory properties, and the test results showed that the extract contained higher levels of phenolics and flav onoids. Various
flavonol glycosides, regularin, quercetin, anthocyanins and various flavonoid-
rich plant extracts are known to have anti-
inflammatory properties, especially against type 2 diabetes. These suggest that there may be a relationship betwe en the rich phenolic
and flavonoid content of the extracts in this study and their antiinflammatory properties. Therefore, the conclusio n from the current
study is that MELS supplementation can effectively control blood sugar levels without causing hyperglycemia; It can improve lipid
metabolism and is a therapeutic strategy to prevent the development of atherosclerosis. Prevention of lipid peroxi dation by potent antioxidant in experimental diabetic rats. Therefore, the pure fraction of methanolic extract of p umpkin can be considered a good anti-
inflammatory agent because of the flavonoid and polyphenol content in the extract. [19]

VIII.CONCLUSION

When two (or more) drugs are taken together, there is a possibility of chemical or drug interactions. This interacti on may change how the drug works, causing more or less benefit or serious side effects. The results depend on m any drugs and medications, such as the
physicochemical properties of the drugs used and how they interact pharmacokinetically and pharmacodynamical ly. Although the
interaction mechanisms between herbs and drugs are similar, they can become more complex when there are mul tiple combinations. Herb
drug interactions (HDI) can affect safety and efficacy through addition/combination or interactions between herb al ingredients
and drug molecules. Although adverse or adverse effects have received more attention due to safety concerns, ad ditive/synergistic
effects of HDIs may still increase the need for effective medications.

8.1Herb drug interactions include:

8.1.1Pharmacokinetic drug-drug interactions:

The main basis of drug interactions drug pharmacokinetic interaction is both induction and inhibition by drug an d drug interactions.

Gastrointestinal and drug interactions. Hepatic metabolic enzymes, such as the CYP family of enzymes, involve drug transport and

protein efflux.

8.1.2Pharmacodynamics Herb-Drug Interactions:

Certain substances in plants can cause interactions between herbs and drugs by acting on the same target drug mo lecules (such as

receptors or enzymes). Antibiotics or antibiotics. .

Synergistic or additive effects can lead to drug toxicity, and longterm negative interactions can lead to drug reduc tion and treatment

failure.Lagenaria siceraria is part of the Cucurbitaceae family and is known as squash. The herb is widely used th roughout India. It is a climbing or creeping herbaceous plant with bottle or dumbbell

shaped fruits. Plane trees and their fruits are often eaten as

vegetables. It has traditionally been used in India, China, European countries, Brazil, Hawaii Island, etc. due to it s cardiotonic, generaltonic and diuretic properties. It is used as medicine in many countries. Additionally, fruit ex tracts have anti-hepatotoxic, analgesic and anti

inflammatory, hypolipidemic, hypoglycemic, immunomodulatory and antioxidant activities.

Lagenaria siceraria fruit is a good source of B complex vitamins, ascorbic acid, fibre, protein, cucurbitacins, sapo nins, fucosterol and complex sterols, polyphenols and flavonoid Cglycosides. The methanol extract of its leaves contains sterols, polyphenols, flavonoids, saponins, proteins and carbohydrates. In diabetes treatment, patients us e herbal medicines containing sulfonylureas, biguanides and

meglitinides, with or without the knowledge of their doctors, to get better results.

This can be beneficial or toxic.More herbs, often used in combination with good medicines. Components in herb al preparations may

be substrates, inhibitors, or inducers of cytochrome P450 enzymes and may aid the metabolism of joint medicati ons.

Pharmacokinetic and pharmacodynamic effects. Studies have also shown interactions between Lagenaria sicerari a extract and various synthetic drugs. Although CYP1A1 is a type of CYP involved in the metabolism of rat Lag enaria siceraria extract and pioglitazone.

Unfortunately, no attempt has been made to study the interaction between Lagenaria siceraria and pioglitazone (b eta carotene, one of

its main components). It is stated that the medicinal plant is related to Lagenaria siceraria and many synthetic dru gs. According to

research data, no herbal interaction has been reported between Lagenaria siceraria and pioglitazone. Therefore, it is necessary to learn the medicinal herbs of this medicine.

These herbal preparations are used by patients who may or may not be aware of the interactions

between herbs. Investigating the herbal interaction between Lagenaria siceraria and the drug pioglitazone is impo rtant for the information of the patient and the doctor.

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