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REVIEW ARTICLE

A REVIEW ON HEPATOPROTECTIVE ACTIVITY

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ABSTRACT

Liver is one of the largest and most vital organs in human body and the chief site for intense metabolism and excretion. It has a surprising role in the maintenance, performance and regulating homeostasis of the body. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction. The major functions of the liver are carbohydrate, protein and fat metabolism, detoxification, secretion of bile and storage of vitamin. Thus, to maintain a healthy liver is a crucial factor for overall health and well-being. But when it is continuously and variedly exposed to environmental toxins, chemicals like CCl4, drug habits, alcohol, infections and autoimmune disorders, prescribed (antibiotics, chemotherapeutic agents) cum over-the-counter drugs can eventually lead to various liver ailments like hepatitis, cirrhosis and alcoholic liver disease. These conditions can be cured with hepatoprotective agents. Both in vitro and in vivo liver models have been developed in the past years to study the hepatoprotective agents. These Systems measures the ability of the test drugs to prevent or cure liver toxicity (induced by various hepatotoxins) in experimental animals.

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INTRODUCTION

The Greek word for liver is hepar, so medicinal terms related to liver often start with hepato or hepatic. Liver plays a pivotal role in metabolism, secretion and storage and is sometimes referred as the " great chemical factory" of the body, because the body depends on the liver to regulate, synthesize, store and secrete many important proteins, nutrients, chemicals and to purify and clear toxins or unnecessary substances from the body. The bile secreted by the liver, among other things, plays an important role in digestion. The risk of the liver intoxication has recently increased by the higher exposure to environmental toxins, pesticides, pharmaceuticals and frequent use of chemotherapeutics. Liver damage is always associated with cellular necrosis, increase in tissue lipid peroxidation and depletion in the tissue glutathione (GSH) levels. In addition, serum levels of many biochemical markers like serum glutamate oxaloacetate transaminase (SGOT/AST) and serum glutamate pyruvate transaminase (SGPT/ALT) triglycerides, cholesterol, bilirubin and alkaline phosphatase are elevated.

The following are some of the liver diseases that are commonly observed.

a) Necrosis
b) Cirrhosis
c) Hepatitis- may be of viral, toxic or deficiency type.
d) Hepatic failure - Acute or chronic
e) Liver disorders due to impaired metabolic function.

Generally the disorders associated with fat (liposis) and bilirubin (jaundice) metabolisms are very commonly seen.

- Disorders associated with fat metabolism: Fatty Liver
- Disorders associated with bilirubin metabolism: jaundice or which may be of different types based upon mechanisms of action and etiology.
  - Hemolytic/Pre-hepatic jaundice
  - Obstructive (post-hepatic / cholestatic jaundice)
  - Hepatogenous/ hepatic jaundice/cholestasis (In these three conditions there occurs unconjugated hyperbilirubinaemia)
  - Hereditary jaundice or pure cholestasis: Gilbert's syndrome, Dubin Johnson syndrome and Crigler-Najjar syndrome etc, Rotor's syndrome are some of the hereditary jaundice types.

f) Chemical/Drug induced hepatotoxicity: Generally may be hepatitis, jaundice and carcinogenesis.

Hepatotoxicity

Hepatotoxin is a toxic chemical substance which damages the liver. Toxic liver injury produced by drugs and chemicals may virtually mimic any form of naturally occurring liver disease.

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Hepatoprotective effect was studied against chemicals and drugs induced hepatotoxicity in rats like alcohol, carbon tetrachloride, galactosamine, paracetamol, isoniazid and rifampicin, antibiotics, peroxidised oil, aflatoxin etc. Severity of hepatotoxicity is greatly increased if the drug is continued after symptoms develop. Among the various inorganic compounds producing hepatotoxicity are arsenic, phosphorus, copper and iron. The organic agents include certain naturally occurring plant toxins such as pyrrolizidine alkaloids, myotoxins and bacterial toxins. Liver injury caused by hepatotoxins, such as carbon tetra chloride (CCl_4), ethanol and acetaminophen, is characterized by varying degrees of hepatocyte degeneration and cell death via either apoptosis or necrosis. The generation of reactive intermediate metabolites from the metabolism of hepatotoxins and the occurrence of reactive oxygen species (ROS) during the inflammatory reaction, account for a variety of pathophysiologic pathways leading to cell death, such as covalent binding, disordered cytosolic calcium homeostasis, GSH depletion, onset of mitochondrial permeability transition (MPT) and associated lipid peroxidation. The metabolism of hepatotoxins by cytochrome P-450 enzyme subtypes is a key step of the intoxication; therefore, enzyme inhibitors are shown to minimize the hepatotoxin-associated liver damage. Moreover, substantial evidence exists that MPT is involved in ROS-associated hepatocellular injury and new findings offer a novel therapeutic approach to attenuate cell damage by blocking the onset of MPT. Thus, oxidant stress and lipid peroxidation are crucial elements leading to hepatotoxin-associated liver injury. In addition to specific treatment for a given hepatotoxin, the general strategy for prevention and treatment of the damage includes reducing the production of reactive metabolites of the hepatotoxins, using anti-oxidative agents and selectively targeting therapeutics to Kupffer cells or hepatocytes for on-going processes, which play a role in mediating a second phase of the injury.

Classification of hepatotoxins

Hepatotoxins are basically classified into two types

They are: Intrinsic and Host idiosyncrasy

Intrinsic

These consist of agents that are predictable hepatotoxins. They are recognized by high incidence of hepatic injury exposed individuals and in experimental animals. There is a consistant latent period between exposure to a particular agent and the development of hepatic injury and the injury appeared to be dose related.

There are two types of intrinsic hepatotoxins:

Direct hapatotoxins

It may be so called because they (metabolic products) produce direct injury to hepatocytes and its organelles, especially the endoplasmic reticulum. CCl4, the prototype, produces peroxidation of the membrane lipids and other chemicals that lead to degeneration of the membranes.

Indirect hepatotoxins

They are anti-metabolites and related compounds that produce hepatic injury by interference with the specific metabolic pathway or processes. The structural injury produced by indirect hepatotoxins, appear to be secondary to a metabolic region. While in that produced by direct hepatotoxins, the metabolic dearrangement is secondary to the structural injury. The hepatic damage produced by indirect hepatotoxins may be mainly cytotoxic injury (by interfering with metabolic pathway or processes essential for parenchyma integrity) expressed as steatiosis or necrosis, or may be mainly cholestasis, interfering only or mainly with biliary secretion.

Host idiosyncrasy

It consists of agents that are not predictably hepatotoxic, but produces hepatic injury in only a small portion of exposed individual. In several instances auto antibodies directed against normal cellular constituents are detected. The injury does not appear to be dose related and is not reproducible in experimental animals and appears after a variable latent period**.**

Evaluation of hepatoprotective activity

Several chemical substances and drugs having specific actions on liver are used as hepatotoxins in experimental animals to simulate ideal diseased conditions. The hepatoprotective activity can be most easily evaluated/screened with the aid of several model systems of liver damage in experimental animals. In all test model systems, conditions for liver damage are implemented and an attempt is made to counteract this toxicosis with the substance/preparation under test. The magnitude of the protective effect can be measured by estimating the enzyme activities and the rate of survival and can be verified histologically. The available methods are in vivo**,** ex vivo and in vitro methods. All these methods are used to study the protective or curative effects of any compound under test. In order to test for hepatoprotective activity the test substance and the hepatotoxin are administered simultaneously whereas in case of antihepatotoxic or curative activity the test substance is generally administered after induction of hepatotoxicity

In vitro methods

Hepatocytes are generally isolated by using in-situ, two step recirculating collagenase perfusion technique. These are then seeded in small containers and exposed to test samples and toxins. After a specified time period, the degree of toxicity or protection is assessed by viability tests and enzyme levels such as GOT and GPT. By employing primary culture hepatocytes using CCl_4, galactosamine, thioacetamide, ethanol, paracetamol (PCML) etc. as hepatotoxins several hepatoprotective screening models have been devised. These have a number of advantages over **in vivo** methods such as their ability to dispose numerous samples at a time, low cost with a small size, little variation and reproducibility of results. The major disadvantage is that sometimes it may not reflect the events which occur in animals.

Ex vivo models

In this model, after completion of preselected in vivo test protocol hepatocytes are isolated and the percentage of viable cells and biochemical parameters are determined as liver function tests. These methods are somewhat better correlated to clinical models than in vitro or in vivo methods.

List of hepatoprotective activity having medicinal plants

Botanical name	Family	Plant parts used	Screening methods
Acacia catechu	Leguminosae	Powdered pale catechu	Carbontetra chloride induced
Acacia confuse	Leguminosae	Bark	Carbon tetra chloride induced
Aegle marmelos Correa	Rutaceae	Leaves	Paracetamol Induced
Aerva lanata	Amaranthaceae	Coarce powder Plant	Paracetamol Induced
Alchornea cordifolia	Euphorbiaceae	Leaves	Paracetamol Induced
Alocasia indica Linn	Araceae	Leaves	Paracetamol Induced
Aloe barbadensis	Liliaceae	Dried aerial parts	Carbontetra chloride induced
Amaranthus spinosus	Amaranthaceae	Whole plant	Carbontetra chloride induced
Amaranthus caudatus Linn	Amaranthaceae	Whole plant	Carbontetrachloride Induced
Anisochilus carnosus Linn	Lamiaceae	Stems	Carbontetrachloride Induced
Apium graveolens	Apiaceae	Seeds	Paracetamol and thioacetamide induced
Arachiodes exilis	Dryppteridaceae	Rhizomes	Carbontetra chloride induced
Argemone mexicana	Solanaceae	Plant material	Carbontetra chloride Induced
Asparagus racemosus Linn	Asparagaceae	Roots	Paracetamol induced
Azadirachta indica	Meliaceae	Leaf	Paracetamol Induced
Azitetracantha	Salvadoraceae	Leaves	Paracetamol induced
Baliospermum montanum	Euphorbiaceae	Roots	Paracetamol induced
Boerhaavia diffusa	Nyctaginaceae	Roots	Thioacetamide induced
Bupleurum kaoi	Umbelliferar	Dried roots	Carbontetra chloride induced
Byrsocarpus coccineus	Connaraceae	Leaf	Carbontetra chloride induced
Bixa orellana	Bixxaceae	Plant material	Carbontetra chloride induced
Cajanus cajan Linn	Leguminosae	Pigeon pea leaf	D-galactosamine induced
Cajanus scarabaeoide	Fabaeceae	Whole plant	Paracetamol induced
Carissa carindas Linn	Apocyanaceae	Root	Carbontetrachloride Induced
Carum copticum	Apiaceae	Seed	Carbontetra chloride,paracetamol induced
Calotropis procera	Asclepediaceae	Root bark	Carbontetrachloride Induced
Cassia fistula	Leguminosae	Leaf	Carbontetrachloride Induced
Cassia tora	Caesalpiniaceae	Leaves	Carbontetra chloride induced
Cassia Occidentalis	Caesalpiniaceae	Leaves	Paracetamol and Ethyl alcohol induced
Chamomile capitula	Asteraceae	Fresh natural mature capitula	Paracetamol induced
Clerodendrum inerme	Verbenaceae	Leaves	Carbontetra chloride induced
Clitoria ternatea Linn	Fabaceae	Leaves	Paracetamol induced
Cleome viscose Linn	Capparidaceae	Leaf powder	Carbon tetra chloride induced
Cochlospermum planchoni	Coclospermaae	Rhizomes	Carbontetra chloride induced
Cichorium intybus	Asteraceae	Leaves	Thioacetamide induced
Cordia Macleodii	Boraginaceae	Leaves	Carbontetra chloride induced
Cuscuta chinensis	Convolvulaceae	Seeds	Acetaminophen induced
Decalepis hamiltonii	Asclepiadaceae	Roots	Carbontetra chloride induced
Elephrantopus scaber Linn	Asteraceae	Whole plant	D-galactosamine and acetaminophen induced
Equisetum arvense	Equisetaceae	Aerial parts	Carbontetra chloride Induced
Embelia ribes	Myrsinaceae	Fruits	Paracetamol induced
Enicostemma axillare	Gentianaceae	Whole plant	D-galactosamine
Euphorbia fusiformis	Euphorbiaceae	Tubers	Rifampicin
Ficus religiosa Linn	Moraceae	Stem bark	Paracetamol induced
Fructus schisandrae	Magnoliaceae	Dried fructus	Carbontetra chloride Induced
Fumaria indica	Papaveraceae	Whole plant	D-galactosamine induced
Ganoderma lucidum	Polyporaceae	Winter mushrooms	D-galactosamine induced
Ginkgo biloba	Ginkgoaceae	Dried extract	Carbontetra chloride Induced
Glyrrhiza glabra	Fabaceae	Root powder	Carbontetra chloride Induced
Gracinia indica Linn	Clusiaceae	Fruit rind	Carbontetrachloride Induced
Gmelina asiatica Linn	Verbenaceae	Aerial parts	Carbontetrachloride Induced
Gundelia tourenfortii	Asteraceae	Fresh edible stalk	Carbontetra chloride Induced
Halenia elliptica	Gentianaceae	Whole plant	Carbontetra chloride Induced
Hibiscus Sabdariffa	Malvaceae	Leaves	Paracetamol induced
Hibiscus esculentus	Malvaceae	Roots	Carbontetra chloride Induced
Hypericum japonicum	Clusiaceae	Whole plant	Carbontetra chloride Induced
Hygrophila auriculata	Acanthaceae	Root	Carbontetra chloride Induced
Hyptis suaveolens Linn	laminaceae	Leaves	Acetaminophen induced
Hoslundia opposite	Lamiaceae	Stem	Carbontetra chloride And paracetamol Induced
Juncus subulatus	Juncaceae	Powdered tubers	Paracetamol induced
Kalanchoe pinnata	Crassulaceae	Leaves	Carbontetra chloride Induced
Lawsonia alba	Lythraceae	Whole plant	Carbon tetrachloride induced
Lactuca indica	Compositae	Aerial parts	Carbontetra chloride Induced
Luffa echinata	Curcubitaceae	Fruits	Carbontetra chloride Induced
Laggera pterodonta	Asteraceae	Whole herb	Carbontetra chloride and D-galactosamine Induced
Mallotus japonicas	Euphorbiaceae	Cortex	Carbontetra chloride Induced
Mamoridca subangulata	Cucurbitaceae	Leaf	Paracetamol induced
Melia azhadirecta Linn	Piperaceae	Leaves	Carbontetrachloride, silymarin induced
Morinda citrifolia Linn	Rubiaceae	Fruit	Streptozotocin induced
Myoporum lactum Linn	myoporaceae	Leaves	Carbontetrachloride Induced
Myrtus communis Linn	Myrtaceae	Leaves	Paracetamol induced
Nelumbo nucifera	Nelumbonaceae	Leaves	Carbontetrachloride Induced

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Nigella sativa	Ranunculaceae	Seeds	Tert –butyl hydroperoxide induced
Ocimum sanctum	Lamiaceae	Leaf	Paracetamol induced
Orthosiphan stamineus	Lamiaceae	Leaves	Acetaminophen induced
Phyllanthus amarus schum	Euphorbiaceae	Aerial part	Ehanol induced
Phyllanthus amarus	Euphorbiaceae	Whole plant except root	Aflatoxin b1 induced liver damage
Physalis minima	Solanaceae	Plant material	Carbontetra chloride induced
Phyllanthus niruri	Euphorbiaceae	Leaves and fruits	Carbontetrachloride Induced
Phyllanthus polyphullus	Euphorbiaceae	Leaves	Acetaminophen induced
Picrorhiza kurrooa	Scrophulariaceae	Root and rhizomes	Alcohol –carbon tetra chloride induced
Picrorrhiza rhizome	Scrophulariaceae	Dried underground stem	Poloxamer(PX)-407 induced
Piper chaba	Piperaceae	Fruit	D-galactosamine induced
Piper longum	Piperaceae	Fruits and roots	Carbontetra chloride induced
Pittosporum neelgherrense	Pittospoaceae	Stem bark	Carbontetra chloride, D-galactosamine and acetaminophen Induced
Plantago major	Plantaginaceae	Seeds	Carbontetra chloride induced
Pterocarpus marsupium	Papilionaceae	Stem bark	Carbontetra chloride induced
Ptrospermum acerifolium	Sterculiaceae	Leaves	Carbontetra chloride induced
Ricinus communis	Euphorbiaceae	Leaves	Carbon tetrachloride induced
Rubia cordifolia	Rubiaceae	Roots	Carbontetra chloride induced
Sarcostemma brevistigma	Asclepiadaceae	Stem	Carbontetra chloride induced
Saururus chinensis	Sauruaceae	Whole plant	Carbontetra chloride induced
Scoparia dulcis	Scrophulariaceae	Whole plant	Carbontetra chloride induced
Schouwia theebica	Arecaceae	Aerial part	Carbontetra chloride induced
Solanum nigram Linn	Solsnaceae	Fruits	Carbontetrachloride Induced
Tecomella undulate	Bignoniaceae	Stem bark	Thioacetamide induced
Tephrosia purpurea Linn	Fabaceae	Aerial parts	Thioacetamide induced
Thunbergia laurifolia	Acanthaceae	Leaves	Ethanol induced
Tridax procumbens	Asteraceae	Leaves	Carbontetrachloride Induced
Tylophora indica	Asclepiadaceae	Leaf powder	Ethanol induced
Vitex trifolia	Verbenaceae	Leaves	Carbontetrachloride Induced
Vitis vinifera	Vitaceae	Leaves	Carbontetrachloride Induced

In vivo methods

This method is used not only to study the nature of the given compound but also to study the mechanism of the toxicant. Hepatotoxicity is produced in experimental animals by the administration of known dose of hepatotoxins like CCl_4, galactosamine, thioacetamide, ethanol and paracetamol etc., which produce marked measurable effects, the magnitude of which can be measured by carrying out various liver function tests viz. morphological, metabolic or functional, biochemical and histopathological determinations. Although it is a very convenient laboratory method, reproducibility of results is rather poor. The compounds having hepatoprotective claims are also evaluated in general for their choleretic or anticholestatic activity in order to know whether the liver disorder is due to an abnormality of bilirubin metabolism or not. Choleretics are those agents which increase the out puts of bile by stimulating the liver where as anticholestatics are those which correct the retention and accumulation of bile due to intrinsic and extrinsic factors in the liver. These activities are evaluated by studying bile flow content in conscious and anaesthetized animals for 5 hours.

Experimental models for hepatoprotective screening

Several chemical reagents and drugs which induce liposis, necrosis, cirrhosis, carcinogenesis and hepatobiliary dysfunctions in experimental animals are classified as hepatotoxins. The following are some of the experimental models explained by employing some of the important hepatotoxins.

CCl_4 model

A number of CCl_4 models are devised depending upon its dosage through different routes of administration.

Acute hepatic damage: Acute liver damage, characterized by ischemia, hydropic degeneration and central necrosis is caused by oral or subcutaneous administration of CCl_4 (1.25ml/kg). The maximum elevation of biochemical parameters are found to be 24 hours after the CCl_4 administration normally administered as 50% v/v solution in liquid paraffin or olive oil.

Chronic reversible hepatic damage: Administration of CCl_4 (1ml/kg S.C.) twice weekly for 8 weeks produces chronic, reversible liver damage.

Chronic, irreversible hepatic damage: Administration of CCl_4 (1ml/kg S.C.) twice weekly for 12 weeks simulates chronic, irreversible liver damage.

Thioacetamide model

Thioacetamide (100mg/kg s.c.) induces acute hepatic damage after 48 hrs of administration by causing sinusoidal congestion and hydropic swelling with increased mitosis.

D-galactosamine model

D-galactosamine (800mg/kg i.p.) induces acute hepatotoxocity after 48 hrs of administration with diffused necrosis and steatosis.

Paracetamol model

Paracetamol induces acute hepatotoxicity depending upon its dosage through different routes of administration, such as

- Paracetamol (800mg/kg i.p.) induces centrilobular necrosis without steatosis.
- Paracetamol at a single dose of 3g/kg p.o. stimulates acute hepatic damage. It takes 48 hrs to induce the toxicity.

Chloroform model

It produces hepatotoxicity with extensive central necrosis, fatty metamorphosis, hepatic cell degeneration and necrosis either

by inhalation or by subcutaneous administration (0.4-1.5ml/kg).

Ethanol model

Ethanol induces liposis to a different degree depending upon its dose, route and period of administration as follows:

- A single dose of ethanol (1ml/kg) induces fatty degeneration.
- Administration of 40%v/v ethanol (2 ml/100g/day p.o.) for 21 days produces fatty liver.
- Administration of country made liquor (3ml/100 g/day p.o.) for 21 days produces liposis.

Hepatoprotective medicaments

A large number of drugs of plant origin are endowed with hepatoprotective claims either directly or indirectly. In recent years, the usage of herbal drugs for the treatment of liver diseases has increased all over the world. The herbal drugs are believed to be harmless and free from serious adverse reactions, as they are obtained from nature and are easily available. Also, the limited therapeutic options and disappointing therapeutic success of modern medicine including herbal preparations. In recent years many researchers have examined the effects of plants used traditionally by many folklore remedies from plant origin have long been used for the treatment of liver diseases indigenous healers and herbalists to support liver function and treat diseases of the liver. In most cases, research has confirmed traditional experience and wisdom by discovering the mechanisms and mode of action of these plants as well as reaffirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies. Several hundred plants have been examined for use in a wide variety of liver disorders. Just a handful has been fairly well researched. There are about 600 commercial herbal formulations, which are claimed to have hepatoprotective activity and many of them are being sold in market all over the world. In India, about 40 patented poly herbal formulations representing a variety of combinations of 93 herbs from 44 families are available. It has been reported that 160 phytoconstituents from 101 plants possess hepatoprotective activity. Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthone derivatives. Studies carried out in China and Japan resulted in the isolation of a hepatoprotective lignan, gomishin from the fruits of Chinese medicinal plant Schizandra chinensis. Gomishin is used for the treatment of chronic hepatitis. Studies carried out at Tropical Botanic Garden and Research Institute (TBGRI) have shown that Trichopus zeylanicus, Phyllanthus maderaspatensis and P. kozhikodianus are extremely active against paracetamol-induced liver damage in rats. A recent report indicates that fumaric acid obtained from Sida cordifolia has significant anti-hepatotoxic activity in rat. Ursolic acid which occurs in many plants also showed promising hepatoprotection against paracetamol and CCl_4 induced liver damage in rats. Some of the reported constituents with pharmacologically/ therapeutically proved claims may be enlisted as silymarin, (+) - catechin, saikosaponins, curcumin, glycyrrhizin, picroside I and II gomisin etc, acetyl bergenin and kolaviron. Most commonly used plants in herbal formulations in India and scientifically validated in experimental animals are Andrographis paniculat), Boerhaavia diffusa, Eclipta alba, Picrorrhiza kurroa, Cichorium intybus and Tinospora cordifolia.

Antioxidants can protect experimental animals and humans from oxidant mediated liver damages. This effect can be seen even in certain common vitamins, spices and vegetables (e.g. Vitamin-E and turmeric). Several plants have been reported to have hepatoprotective activity among those, a few plants tested against different experimental models are listed in below table.

Conclusion

Despite tremendous advances in modern medicine, hepatic disease remains a worldwide health problem; thus the search for new medicines is still ongoing. Numerous formulations of medicinal plants are used to treat liver disorders in Chinese ethno medical practice and traditional medicine. Many of these treatments act as radical scavengers, whereas others are enzyme inhibitors or mitogens. The hepatoprotective activity of the plants probably due to the presence of flavonoids, alkaloids, terpenoids, glycosides and steroids. Active extracts, fractions or mixture of fractions/extracts of Plants may prove very effective drugs. Plant drugs (combinations or individual drug) for liver diseases should possess sufficient efficacy to cure severe liver diseases caused by toxic chemicals, viruses (Hepatitis B, Hepatitis C, etc.), excess alcohol intake, and repeated administration of drugs like paracetamol, Rifampicin and Isoniazid. A single drug cannot be effective against all types of severe liver diseases. Effective formulations have to be developed using indigenous medicinal plants, with proper pharmacological experiments and clinical trials. The manufacture of plant products should be governed by standards of safety and efficacy.

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