INTEGRATED REVIEW OF HEPATOPROTECTIVE AND HEPATOTOXIC DRUG

Amitabh Sharma[1], Surya Prakash Gupta[2], Abu Tahir[3*]

Abstract:
It was shown that Polygonum persicaria lessened the liver damage caused by CCl4. Five groups of twenty albino wistar rats were created: control, CCl4-induced hepatotoxicity, and hepatotoxicity using 200 and 400 mg/kg body weight of Polygonum persicaria. After 14 days, the rats were scarified. Twelve rats were used in the toxicity experiments.
Three groups were created at random for the participants: control, 200 and 400 mg/kg Polygonum persicaria, and one group receiving standard silymarin treatment. Samples of blood were drawn for biochemical analysis. Rats in the CCl4-induced hepatotoxic group exhibited mean serum concentrations of AST, ALT, ALP, and TB that were considerably greater than those in the control group ($P<0.001$). Polygonum persicaria treatment groups showed notable decreases in several metrics. Anemia was noted in the CCl4-treated group. Rats given CCl4 treatment experienced less significant hepatic fatty changes. Except for a few isolated fatty changes in the liver at higher doses, same amounts of the plant had no effect on the parameters evaluated above. The presence of liver injury was confirmed by histological changes.
Natural hepatoprotective products include chamomile capitula, and Andrographic paniculata. Marianum Silybum StecheamichuacanaCoccinia grandis Flacourtia indica Calendula Wedelia Annona squamosa, Carica ficus Lepidium vulgare, Solanum nigrum, Swertia chirata, Polycystum sargassum, Given that Phellodendronemblica Combining Picrorhizakurroa with Curcuma longa Azadirachta indica, Aegle MarmelosRoxburghii Cassia Astragalus staminus, Curcas jatropha Foeniculum vulgare, Foenum graecum, Alba Eclipta, Trigonella, The Garcinia mangostana Linn is reviewed.

Keywords: CCl4, Hepatoprotective, Polygonum persicaria, Silymarin, Biochemical analysis, Histopathology.

[1,2,3*]Rajiv Gandhi Institute of Pharmacy, Faculty of Pharmaceutical Science & Technology AKS University, Satna-485001 (MP)

***Corresponding Author:** Mr. Abu Tahir
*Assistant Professor, Rajiv Gandhi Institute of Pharmacy, Faculty of Pharmaceutical Science & Technology AKS University Satna (MP)-India-485001, Email ID: aliabutahir2009@gmail.com

DOI: 10.53555/ecb/2022.11.9.155

Introduction:

The liver is the biggest and most complex internal organ in living systems. Its many different roles contribute significantly to the upkeep of the interior environment. It contributes to the intermediate state metabolism of lipids, proteins, and carbohydrates. Metals, proteins, glycogen, and other vitamins are stored in it. It also aids in controlling blood volume by transferring blood from the portal to the systemic circulation. It also contains reticuloendothelial system, which is part of immune system. During detoxification, it is necessary for the excretion of various endogenous and foreign toxins. The most prevalent and lethal cause of sickness and mortality worldwide is liver disease [1]. One of the most significant organs in the human body, the liver regulates metabolism and is also in charge of secretion, storage, and detoxification[2]. Hepatotoxin-associated liver injury affects bile excretion, which is reflected in elevated serum toxin levels[3]. Managing liver disorders remains a challenge to contemporary medicine, as they remain one of the most serious health conditions. Alcohol consumption, nonalcoholic fatty liver disease, and the hepatitis C/B virus are the three most prevalent causes of liver disease. Oxidative stress is a known cause of liver disease, although it can be avoided with the use of antioxidant hepatoprotective medications. It has been demonstrated that free radicals can cause oxidative stress[4]. Hepatic disease, sometimes referred to as liver disease, is a disorder that affects the tissues, cells, structures, or activities of the liver[5].

According to estimates from the World Health Organization (WHO), cirrhosis is responsible for around 800,000 of the 2.4 million liver disease-related deaths that take place annually.But according to epidemiological studies conducted by Mexico's National Institute of Statistics and Geography (INEGI, for short), over 600,000 deaths were recorded there in 2013. 14.25 percent of the reasons were diabetes mellitus, followed in order by ischemic heart disease (12.63%), cerebrovascular disease (5.29%), and liver disease (4.79%). Notwithstanding the creation of new hepatoprotective drugs and the developments in modern medicine[6].

The successful development of liver therapeutics requires the availability of both in vitro and in vivo test model systems for hepatic injury. There are several models available to assess the antihepatotoxic activity of a drug. Owing to the limitations included in every model, it is essential to utilize a blend of approaches to guarantee the accuracy of the findings. In research and/or clinical settings, examples of the application of synthetic compounds or pure or semi-purified chemicals obtained from herbal sources with proven hepatoprotective properties in a range of in vitro and in vivo models are provided. The findings may make it easier to conduct further studies in both experimental and clinical settings on hepatotoxic and hepatoprotective medications.

These advances have produced new opportunities as well as challenges for translational research, since they have led to the identification of multiple inflammatory targets that may be therapeutically intervened against in various forms of liver injury through the use of specific drugs[7].

Hepatic injury is the cause of necrosis, jaundice, fibrosis, cirrhosis, hepatitis, liver cancer, and other conditions[8]. The effects of the substance can be genotoxic (nitrogen mustard induces neoplasia), pathological (paracetamol causes liver injury), or pharmacological (barbarites create excessive central nervous system depression). Pharmacological toxicity or unfavorable effects from these interactions can be prevented by reducing the concentration of the drug or chemical in the tissues through metabolism or excretion from the body [9].

Recent experience has shown that plant drugs are generally safe, non-toxic, and even free of significant side effects[10].

CLASSIFICATION:

These are generally categorized into three types without any discernible differences between them.

Anti-hepatotoxic drugs: These frequently mitigate the effects of hepatotoxins that cause hepatitis or liver damage.

Hepatotropic substances: They frequently support or ease the liver's repair process. It is actually hard to distinguish between these two activities.

Hepatoprotective agents: They frequently guard against a range of liver disorders. Every hepatoprotective drug has the ability to act as an anti-hepatotoxic or hepatotropic agent, albeit this is not always the case.

TREATMENT OF LIVER DISEASE:

Each liver disease will have a unique treatment plan. For example, in order to keep the patient hydrated while the body's immune system battles

and eliminates the virus, supportive care is required for hepatitis A. Patients with gallstones may require surgery to remove the gallbladder. For certain illnesses, long-term medical care may be required to control and mitigate symptoms. Patients with cirrhosis and end-stage liver disease may require medication to control how much protein is absorbed from the diet.

Liver disease caused by cirrhosis may impede the liver's ability to metabolize waste products, potentially resulting in elevated blood ammonia levels and hepatic encephalopathy. A low-sodium diet and water pills (diuretics) may be required to lessen water retention.

Paracentesis, or the use of a needle and syringe to remove excess fluid from individuals with excessive ascites fluid, may occasionally be required. Under local anesthetic, a needle is inserted through the abdomen wall to extract the fluid. There may be a need for procedures to address portal hypertension and lower the risk of bleeding. The liver is the only option left to patients whose livers are failing.

HERBAL TREATMENT:

One important source of hepatoprotective medications is medicinal plants. Herbal remedies including one or more plants have been used to treat liver diseases. More than 700 herbal preparations, both mono and poly, are purportedly available for therapeutic use as tinctures, tablets, capsules, and decoctions prepared from more than 100 plants. Hepatoprotective drugs are those that are good for the liver. Conversely, medications that cause harm to the liver are referred to as hepatotoxic medications. Additionally, studies have demonstrated the efficacy of herbal remedies in the management of liver conditions. The research on herbal remedies that are helpful for gall bladder and liver problems is covered in this article.

HEPATOPROTECTIVE HERBS:

Leading pharmaceutical companies have helped herbal therapies for liver diseases become more well-known worldwide. They have been used for a very long time in India. Even while a number of herbal remedies are very well-liked in general and for liver ailments specifically, they are still not suitable therapy options for liver diseases. The following limiting elements contribute to this eventuality:

- Herbal drug standardization is lacking.
- Inability to identify the active ingredient or principles.
- There aren't enough RCTs, or randomized controlled trials.
- Insufficient toxicological analysis.

Polyherbal treatment:

- Milk Thistle (Silybum marianum)
- Turmeric (Curcuma longa)
- Licorice (Glycyrrhiza glabra)
- Dandelion (Taraxacum officinale)
- Schisandra (Schisandra chinensis)
- Ginger (Zingiber officinale)
- Burdock (Arctium lappa)
- Artichoke (Cynara scolymus)
- Picrorhiza (Picrorhizakurroa)
- Andrographis (Andrographis paniculata)

Evaluation models:

Nearly all acute and chronic liver ailments, including cirrhosis, cholestasis, necrosis, and hepatic traumas, are able to be chemically induced. All of these can be generated with different liver damage models.

Hepatoprotective models use the compounds, fractions, or extracts that are being studied to try and stop or lessen the damage that hepatotoxins cause. The amount of the hepatoprotective effect can be determined by looking at the liver's histology, survival rate, and biochemical indicators.

Test techniques like in vitro, ex vivo, or in vivo (table 1) can be used to assess if a material is hepatoprotective or hepatocurative, depending on whether the hepatoprotective agent is administered prior to or following the hepatotoxin. [31]

Table 1. Models of evaluations of hepatoprotective activity.

Model	Examples	Advantages	Disadvatages
In vitro	.Fresh hepatocytes .Primary hepatocyte culture .Immortalized cell lines (HepG2, HUH7, HepRG)	. Quick and cheap tests .Requires few samples . High control of variables; reproducible .Can analyses various samples in the same test	. Due to a lack of complexity present in the organ of biological system, results should be interpreted with caution. . Samples do not undergo any biotransformation process

Ex vivo	.Precise liver cuts . Isolated perfused liver	. Resemble the *in vivo* environment . Decrease the number of animals experimented on .A human tissue model can be developed	. Low oxygenation rate in the internal cells . Low cut viability (1–10 días) . There are significant differences in size and fuction between human and murine tissue.
In vivo	. Murine model	.Widely used . There is a greater correlation with what happens in humans . All biochemical and histological parameters can be measured	. Requires a large number of animals to experiment on . Interindividual variation exists . A larger simple size is required . Large and expensive experiments

***In vitro* models:**

Primary hepatocyte cultures, fresh hepatocytes, and immortalized cell lines are used to evaluate the hepatoprotective impact. Action mechanisms can be established in these models. The cellular and molecular mechanisms of action can be determined using these models, which are the most efficient means of selecting and screening potential hepatoprotective medications.[11, 12, 13]

To evaluate protection, measurements are taken of things like transaminase release, cell multiplication, morphology, oxygen consumption, macromolecular synthesis, etc.[13, 14, 15]

Advantages of *in vitro* models are: They are considered repeatable tests because they can be finished in two to three testing days, only need small amounts of the test substance (milligram range), give strict control over the experimental setup, analyze multiple samples in one test, are affordable, and have low variability. Primary cultures or fresh hepatocytes require less experimental animals than do in vivo models.

Disadvantages of *in vitro* models: It is crucial to keep in mind that an organism's cells form complex, personal networks with the extracellular matrix and with one another. It is imperative to verify this in vivo systems and consider it when interpreting results from in vitro investigations. Cell differentiation occurs more quickly in isolated cells and cell lines because of the lack of their natural environment. The body's normal absorption and dispersion mechanisms do not occur for the substances used in the testing. There is little to no cell-to-cell interaction and the organ is inherently very complicated.[13, 16, 17, 18, 19]

Ex vivo models:

Precision-cut liver slices (PCLS) are an ex vivo tissue culture that replicates the multicellular characteristics of in vivo organs. This approach allows for morphological studies and preserves spatial disposition and cellular interaction. Liver slices are a valuable ex vivo model for investigating metabolism and liver injury and can act as a bridge between in vivo systems and cell cultures since they can sustain the biliary canaliculus and metabolizing enzymes[18].[19]

Isolated and perfused liver transplants are utilized as a model to integrate in vivo circumstances with in vitro characteristics. Pig livers were utilized to make the first model, and later smaller species (rats, mice, and rabbits) were used. This model preserves the tridimensional structure and cell-to-cell interactions while permitting the real-time collecting of bile. If blood is used as a perfusor liquid, hemodynamic parameters can be studied[20].

Advantages of *ex vivo* models:These are low-cost, replicable models that replicate in vivo settings. Less experimental animals are utilized in PCLS, and the model can be constructed using human organs.

Disadvantages of *ex vivo* models: Examining the biliary flow or functional elements such as portal flow is not feasible in PCLS. The slices only have an 8–10 day viability period due to inadequate oxygen and food transport to the more inner cells, even with the development of novel culture techniques. Because of space and financial limitations, perfused rat liver is the best option for small labs; nonetheless, the anatomy, physiology, and size of the murine liver are very different from those of the human liver.[13]

***In vivo* model:**

With this widely used model, we are able to determine the protective mechanism. Various biochemical and metabolic indicators as well as histological analyses are utilized to determine the level of harm and/or protection inflicted on experimental animals by known dosages of different hepatotoxins.[13, 21]

Advantages of *in vivo* models: is the model that allows for the measurement of all biochemical and histological parameters and most closely mimics human activity. They allow us to speculate about the possible contributions of the central nervous system and immune system to the development of hepatic diseases.

Disadvantages of *in vivo* models: They take a long time to manufacture and frequently require a large number of animals, which raises ethical and financial difficulties. While a number of liver diseases have been modeled, there are considerable differences in the molecular pathophysiology between the human species and the model as well as inter-individual variance. They require a larger sample size to do the experiment, which could be a limitation, especially when looking at natural materials.[13, 22]

Hepatotoxic agents and their mechanism of action:

The compounds that harm the liver are called hepatotoxins; by using different chemicals and drugs, it is now feasible to simulate any kind of hepatic disease that has a natural origin.

Hepatotoxins, including ethanol, thioacetamide, carbon tetrachloride {CCl4}, and acetaminophen, can be classified as intrinsic if they cause dose-dependent harm, exhibit a continuous delay between exposure and the commencement of liver injury, or have a predictable mechanism of action. Unpredictable, causing liver damage in a small proportion of exposed individuals, dose-independent, developing after a variable latent time, and non-replicable in experimental animals are characteristics of idiosyncratic agents.[13, 23, 24]

Carbon tetrachloride (CCl_4)

The toxicity of CCl4 depends on the duration and quantity of exposure. Lipid peroxidation, cytokine release, disruption of Ca2+ homeostasis, and the possibility of apoptotic events that are followed by cellular regeneration are among the effects at low doses. In circumstances of big dosages, continuous exposure, more severe repercussions, and longer-lasting injury, patients may develop fibrosis, cirrhosis, or even cancer.

Cytochrome P450-dependent monooxygenases primarily metabolize CCl4 via the endoplasmic reticulum and mitochondria-resident CYP2E1 isoform.[25] The formation of highly reactive trichloromethyl radicals (CCl3) is what causes hepatotoxicity. These reactive oxygen species have the ability to damage unsaturated fatty acids and induce lipid peroxidation, which can overwhelm the body's antioxidant defense mechanism. They can also alter the balance of water and electrolytes, raise the levels of hepatic enzymes in plasma, and decrease the amount of cytochrome P450, which can result in a functional failure and a subsequent decrease in protein and triglyceride buildup (fatty liver).[26] Lipid peroxidation sets off a chain of events that lead to endogenous hazardous chemical synthesis and further hepatic dysfunction and difficulties. These events include the breakdown of membrane lipids. Thus, it is believed that lipid peroxidation plays a significant role in the pathogenesis of CCl4-induced liver injury. Limiting the generation of the radical CCl3 is one of the most crucial tactics for mitigating the damage. For this reason, many businesses use this approach to evaluate pharmaceutical and natural products with hepatoprotective and antioxidant qualities.[27, 28]

Ethanol:

The liver is the organ most susceptible to the negative effects of ethanol. Oxidative stress is brought on by the metabolism of ethanol by the cytochrome P450 CYP2E1 isoform, which raises lipid peroxidation and generates reactive oxygen species. This modifies the cellular membrane's phospholipid makeup. The damage mechanism is as follows.[29, 30] When membrane lipid peroxidation loses its shape and integrity, serum levels of glutamyl-transpeptidase, an enzyme that bonds membranes, rise. Catalase, glutathione peroxidase, and dismutase superoxide all become less active when exposed to ethanol[12]. It is believed that the antioxidant enzymes dismutase superoxide and peroxidase glutathione become less active due to the harmful effects of free radicals produced after exposure to ethanol. On the other hand, it's feasible that the ethanol oxidation byproduct acetaldehyde is directly to blame for this decline in activity.

Definition of barley, fennel seeds ,papaya and polygonum:-

Barley:

Since ancient times, barley (Hordeum vulgare, family Poaceae) has been one of the most significant food grains. In terms of output volume and global cultivated area, it ranks fourth among cereals and covers more than 70 million hectares of land globally[32]. Barley can be grown as a hullless or hulled crop in two, six, or

seven rows for spring or winter. Based on the grain composition, barley can also be classified as normal, waxy, or high amylose starch, high lysine, high β-glucan, or proantho-cyanidin-free [33].Barley without the hull has a higher nutritional value than barley with the hull because it contains more proteins, lipids, and soluble dietary fiber. The distinct physical and chemical characteristics of various barley types affect how they grow and perform in the end [34].

Barley has been grown in India for thousands of years, and it is considered a sacred crop there. In India, barley is grown on about 6.95 lakh acres, yielding 17.43 lakh tonnes at a productivity of 2508 kg/ha. The principal Indian states that grow barley include Rajasthan, Uttar Pradesh, Haryana, Punjab, Madhya Pradesh, Uttarakhand, Himachal Pradesh, Bihar, Jammu and Kashmir, West Bengal, Chhattisgarh, and Sikkim [35]. In developing countries like India, barley straw is frequently utilized as animal feed [36]. Barley straw is also used as animal bedding and to cover the roofs of huts. Barley is also made into silage or given to animals raw as green feed. It has a lot of potential to be a high-end cereal.Plant breeding has generated cultivars specifically suited for malting. The greatest yielding of these subsequent categories is usually noted. Some countries, like Ethiopia and Nepal, use some grains directly for human nourishment, however this is a relatively limited utilization. The goal of malting varieties is to have a specific grain composition with low protein and β-glucan content and high enzyme activity; however, the environment in which the variety is grown also affects the final product.

Resistant starch, tocols, and glucan are abundant in barley grains and are all beneficial to your health. Barley glucan improves intestinal health by lowering blood sugar and cholesterol. While resistant starch can lower serum cholesterol, tocols can promote intestinal health and lower blood sugar [37, 38, 39]. A barley kernel typically weighs 35 milligrams. The pericarp, germ, and endosperm of barley and oats are situated behind the hull, just like in wheat. Certain varieties of barley and oat that are referred to as "naked" or "hull-less" lack the outer hull, much as wheat kernels do not. These cultivars are unfit for human consumption due to the high lignin and fiber content of their hulls, but they are often used to make functional food products. The oat caryopsis, sometimes called groat, is similar in appearance to the wheat kernel, with the exception that one of its ends is covered in many structures that resemble hairs [39, 40].

Barley grains have the highest functional value, the lowest GI, the most β-glucans, resistant starch, and antioxidant properties of all cereal crops. Soluble fiber-glucans are polysaccharides found in seaweed, barley, oats, mushrooms, and yeasts. Qingke, or hulless barley, is a staple food of the Tibetan people and a major source of feed for livestock. It grows on the Qinghai-Tibetan Plateau, which has many gene families related to stress reactions, particularly different antioxidant capacities due to some polysaccharide and phytochemical compositions. Over the past ten years, there has been a shift in people's eating patterns, which has raised demand for rapid food composition[40].

The nineteenth century:

First attempt at classification: Spanish botanist Claudio Boutelou categorized cultivated barleys into eight classes in 1818:

Hordeum vulgare L., usually referred to as cebadacomún or alcacer, is a kind of barley that is frequently fed to animals. Barley in six rows, spikes fashioned like squares. Winter is the best time to grow it, however spring is when it's most commonly grown. Pale yellow, blue, and black are the colors of spikes.

The spikes on Hordeum hexasticum L. (also known as cebadaramosa, "branched barley"; hexagonal, or seis carreras, "six-row") are both tight and loose.

Rarely was naked barley grown in Spain; it was called Hordeum coeleste L. (cebadadesnuda, "naked barley," or celeste, "sky blue"). The bearded and the trifurcada (a three-part spike) are its two main varieties.

Hordeum distichum L., also known as cebadapamula, ladilla, or de dos carreras, is a kind of barley that is widely grown throughout Europe but is only sowed in Catalonia, Navarra, and Castilla. These were all landraces from Spain, but new, better foreign cultivars of this kind with good malting quality (Hanna from Central Europe and Chevallier and Imperial from the United Kingdom) began to displace them at the turn of the 20th century.

Seldom grown in Spain, Hordeum zeocriton L., sometimes known as "fan barley" or cebada de abanico, is a particularly rustic kind of barley.

The barley Hordeum nigrum has dark glumes and awns.

Hordeum hexasticum β nudum is a six-row barley that is not covered.

Naked barley, or Hordeum distichum β nudum, is another name for it.

The twentieth century:

New varieties gradually replace ancient landraces: New methods of plant breeding were made possible in 1900 by the discovery of Mendel's genetic laws. Based on genetic principles, barley breeding projects have been established in France, Germany, the United Kingdom, and the Netherlands since the turn of the century. The cultivar Hâtif de Grignon, a six-row winter barley that develops early and yields well, was acquired in 1937 thanks to a French initiative. Other six-row winter barley cultivars grown in France are Ager, Barberousse, and Esterel (Doré and Varoquaux, 2006). All ofthese French six-row varieties are very popular in Spain. Both commercial enterprises and the state sector (such as INRA in France) made contributions to the breeding effort.

A shift in variety preference toward malting types, mainly two-row spring cultivars, which were some of the landmarks in barley breeding in Europe, including Spain, was brought about by the decline of animal-drawn transportation and machinery in the twentieth century and the rise in the consumption of barley beer in the Western world (Doré and Varoquaux, 2006).

Beka: obtained by SECOBRA (France, 1954).
Pallas: obtained by Svalof (Sweden, 1958).
Ceres: obtained by INRA (France, 1962).
Julia: obtained by Cebeco (The Netherlands, 1969).
Triumph: obtained by VEB (Germany, 1973).
Alexis: obtained by Breun (Germany, 1987).
Vodka: obtained by Florimond Desprez (France, 1991).
Pewter: obtained by Syngenta (Switzerland, 2002).

On the other hand, the process of creating new cultivars in Spain through crossing and selection was not very successful. The most popular varieties in Spain in the 1950s and 60s were: (García-Fernández, 1958; Mela, 1966).

Cebada común (common barley), desnuda (naked), negra de seis carreras (six-row black), trifurcada (three parts), and cuadrada (square) are examples of traditional Spanish landraces.

There are several types of beer barley that are imported from abroad, including Aurora, Herta, Beka, Etoile de Velay, Foma, Freva, Mari, Pallas, Pioneer, Piroline, and Sonia.

Albacete, Almunia, Atlas, Berta, Cerro, Granja de Ejea, Guadiana, Keka, Lupe, Pané, and Wisa are available for animal food; some are cultivated locally, while the remainder are imported.[41]

Figure 1-Multi-barley seeds in one image.

Phytochemicals in barley: Variable levels of a wide range of phytochemicals, or non-nutrient components, are present in barley and are frequently influenced by environmental or genotypic variables, or both [42]. Barley has a variety of free, conjugated, and bonded phytochemicals that fall into several broad categories, such as phytosterols, phenolic acids, flavonoids, lignans, tocols, and folates.[43]

Histopathological Studies:

10% formalin was used to fix tissue sections from the thoracic aorta. After being cleaned with xylene, the cleansed tissue was dehydrated using isopropanol in descending grades. Subsequently, the tissue was immersed in molten paraffin wax. Hematoxylin and eosin was used to stain sections after they were cut to a thickness of 5 m. After that, the sections were inspected for

histopathological changes using a light microscope (DM RXE, Leica, Germany). In each section, the lumen area and wall thickness at 0, 90, 180, and 270° were measured, and the average was computed.

Analytical statistics The Statistical Package for Social Science 11.0, or SPSS/PC, was used to conduct the statistical analysis. The information was displayed as mean 8 SEM. The significance of differences between mean values was assessed using a one-way analysis of variance (ANOVA) and Duncan's multiple range test, with a significance level of p! 0.05.[44]

Fennel:

Fennel has been used in medicine and cooking for a very long time. Not only can the entire plant be used medicinally, but its extended base may also be used as a vegetable, its leaves can be utilized in cooking, and its seeds can be used and extracted essential oils from. Yellow and brown hues are frequently produced using the flowers and leaves. The most potent form of fennel is pollen, but the cost is considerable. Early Sanskrit literature referred to fennel as madhurika, and it is thought that cultivation of the plant started in India before 2000 BC. Fennel was associated with success and the word "marathon" in Greek mythology. The Battle of Marathon (490 BC) took place in a field of fennel, hence the name.

For the Romans, fennel also symbolized success, and their winners were crowned with the leaves of the plant. The tenth-century manuscript, which documents the pagan Anglo-Saxon Nine Herbs Charm, lists nine plants, including fennel, which is an English word derived from the Old English fenol, or fi nol. Throughout the thirteenth century, fennel was served to monarchs in England as a regal spice along with bread, fruit, and specialties like pickled fish seasoned with fennel.[45]

Edible fennel is frequently used in sauces, liqueurs, sweets, and savory recipes. The plant is widely used in the global culinary and medicinal industries. Copper, iron, calcium, potassium, manganese, selenium, zinc, and magnesium are all present in significant proportions in fennel seeds. The seeds do contain a number of important vitamins, including as vitamins A, E, and C, and a number of B-complex elements, including niacin, pyridoxine, thiamine, and riboflavin [46].

Classification:

Fennel, or the genus Foeniculum, is a member of the Apiales order and family of plants. F. vulgare Mill. vars. piperitum (Ucria) Cout. (bitter fennel), dulce DC Batt. et Trab. (sweet fennel), and azoricum Thell. (sweet fennel) are the three main varieties that have been reported. While Florence fennel is grown for its extended leaf base (which is consumed as a vegetable), leaves (which are used in cooking), and fruits are the main reasons for producing bitter fennel. Planting sweet fennel is done for its fruits, increased leaf base, and fruit-extractable essential oil. Variants of fennel are classified as biennial or perennial aromatic herbs by Weiss (2002), however other authors make a distinction between annual, biennial, and perennial varieties. The somatic chromosomal number of foeniculum, a crop that is cross-pollinated, is 2n=22.[45]

Figure 1. fennel seeds (A)

Phytochemicals in fennel:
For in vitro investigation, such as phytochemical screening and antioxidant testing, powdered flaxseed and fennel seed extracts were dissolved in their corresponding solvents (ethanol 80%, acetone 80%, and water).[46]

Antioxidant activity assays:[47]
DPPH radical scavenging activity: Made up of fixed free radical molecules, DPPH is a black, crystalline powder. To test for antioxidant activity, several extracts were prepared in triplicate using a standard ascorbic acid concentration. The control solution was made with methanol as opposed to the extract. The ability of compounds and extracts to atomize hydrogen or electrons was tested using an illuminating DPPH violet solution. We made 3.9 ml of DPPH Stokes for this technique, added 100 µl of concentrations for each sample, and let the mixture sit in the dark for half an hour.
Through the use of an ultraviolet-vis spectrophotometer, absorbance was determined at 516 nm. The IC50 was then used to express the results. The concentration of substrate that results in a 50% reduction of DPPH activity is known as the factor IC50, which is used to define the DPPH assay results.
The antioxidant activity of the sample was calculated with the following formula:

$$\text{Antioxidant effect\%} = [\,1 - (\frac{\text{Sample absorbance}}{\text{Control absorbance}})] \times 100$$

Papaya:
The papaya fruit is rich in vitamins A and C and is considered to be very nutritious. The total papaya production worldwide in 2013 was 1.25 × 107 metric tons [48]. Errors in fruit classification and quality rating through visual examination might be caused by external variables like fatigue, retaliation, and bias. Variations in visual perception lead to errors in fruit classification in the fruit industry, even with highly competent operators. Consequently, in order to evaluate the fruits and produce more precise data, an automated approach is required[50]. The quality of fruit for eating and how long it takes to preserve it before eating are correlated with its mature state [51]. It takes a long time and is dangerous for human operators to determine these qualities. Thus, in this application sector, prompt, astute, and non-destructive methods are needed [52]. Based on their maturity stage, papaya fruits are divided into three groups in this study.

Numerous academics have published their findings about the prediction of different fruits' ripeness states. It is suggested to use a fuzzy model [53] to assess the level of pineapple fruit ripeness. These are the features that were extracted from CIE Lab* and the hue channel. The fuzzy model was optimized once more using particle swarm optimization, and this time it achieved 93.11% accuracy.
Three stages of banana fruit maturity are distinguished by means of two automated techniques: mean color intensity and area feature [54]. For classification, GLCM and geometrical properties are used. One hundred and twenty pictures of banana fruit—forty of them young, forty ripe, and forty overripe—are used to test the algorithms. The analysis shows that the biggest influences on classification are the average color and size of the banana fruit. With 99.1% accuracy, the mean color intensity algorithm identified the three stages of banana maturity. It was also noted that the area feature algorithm had a flaw in that it could not distinguish between banana fruits that were mature and those that were overmature. Mango fruits were sorted using a procedure that separated them into four groups according to the degree of maturity [55].
categorization, an iterative function Video was captured by the charge-coupled device (CCD) camera from a mango conveyer belt. Next, 27 features are extracted from the video signal frame that was recorded. Based on support vector machines (SVMs), a removal method was employed. With 16,400 photographs evaluated, the system reaches 96% accuracy. Based on their maturity condition, oil palm fruits in a bunch were classified into three categories using a portable four-band sensing system [56]. Four spectral bands—570, 670, 750, and 870 nm—are present in the system.
With 120 oil palm fruit bunches, the discriminant analysis using the Mahalanobis distance classifier yielded an accuracy of 85% using spectral data. A different model (57) was put up that uses multispectral imaging to categorize strawberry ripeness states and estimate quality features. In this case, two techniques were applied: support vector machines (SVM) and principal component analysis with backpropagation neural networks (PCA-BPNN). On a dataset of 280 images, SVM was shown to have the greatest accuracy of 100% for ripeness stage classification.To forecast the ripeness of durian fruit, a non-invasive and non-destructive sensor system has been created [58]. The technique achieved 92.7% accuracy in predicting maturity by utilizing the rician k-factor and the concept of wireless

communication. Using image processing techniques, a maturity classification model for plum fruit is proposed [59].

Classification:
Two methods are used to classify the maturity stage of papaya fruit: machine learning and transfer learning. Table 1 and Figure 1 illustrate how flesh color is used to characterize the maturity level. Appropriate subsections address the details of sample collection and proposed classification models for both strategies.

Table 1 shows the maturity stages of papaya fruits' visual characteristics.

Maturity Stage	**Descriptions**
Immature	Green skin without yellow stripe
Partially Mature	Green skin with well-defined yellow stripe
Mature	Skin clearly yellow in colour and may or may not presence of small light green areas

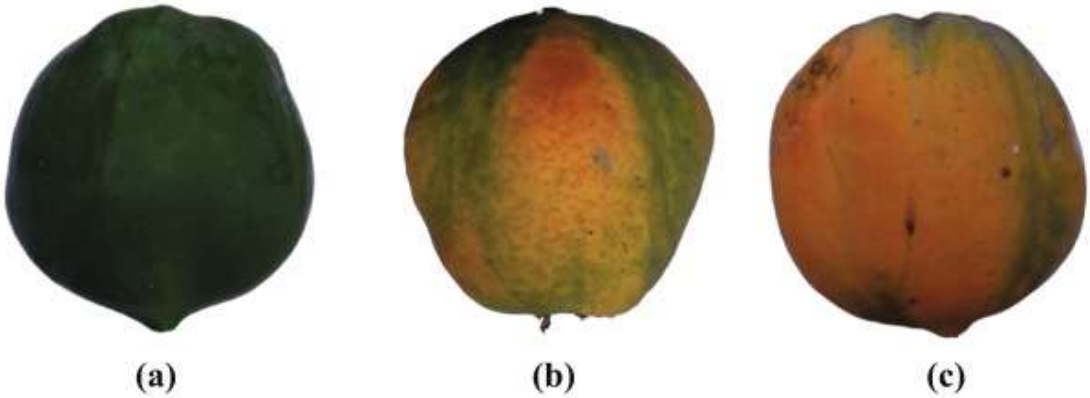

Fig. 1. Papaya Fruits with three maturity stages. (a) Immature (b) Partially Mature (c) Mature.

Cultural practices:
The water and nutrient supply of the plant is influenced by various factors such as soil type, mulching, irrigation, and fertilization. These factors might alter the nutritional content of plant sections that are harvested. However, the impacts of fertilizer-induced mineral and elemental absorption on plants are significant and diverse. Fruit with high calcium uptake has been shown to have longer shelf lives because to decreased respiration rates and ethylene production, delayed ripening, increased firmness, and decreased frequency of physiological illnesses and decay. Conversely, a high nitrogen content is usually linked to a shorter shelf life because of its increased vulnerability to deterioration, physiological issues, and mechanical damage.Papayas that are overfed with nitrogen yield soft fruit.

Nutritional compositions of papaya fruit: An overview
Vitamins A, B1, B, and C are present in papaya in large proportions (Marisa, 2006; Jurandi and Angela, 2011; Laura et al., 2011; Savarni et al., 2011). Additionally high in glucose, fructose, and sucrose is the papaya fruit (Jurandi and Angela, 2011). The nutritional makeup of Rainbow papaya, the first commercially transgenic fruit crop, was described by Savarni et al. (2011). According to Ralf et al. (2011), the most common pigments in papaya fruit during the early stages of carotenoid formation were esterified xanthophylls, such as caprate and β-cryptoxanthin laurate. The study discovered a correlation between fruit maturity and elevated amounts of carotenoids, such as total lycopene and β-cryptoxanthin laurate. On the other hand, esters are mostly responsible for the aroma of papayas, with ethyl butanoate, ethyl acetate, ethyl hexaonate, and ethyl 2-methyl butanoate being the most noticeable odor components. Due to research on the potential health benefits of eating ripe papaya fruit, the fruit is also known as a functional food fruit. For instance, according to Jurandi and Angela (2011), papaya has been used pharmacologically as a meat tenderizer, laxative, and antifertility medication, among other uses.[60]

Plant material:
The voucher specimen for the young papaya leaves was placed in the Department of Pharmaceutical Sciences, Regional Institute of Medical Sciences and Research, Kottayam, after they were collected and identified from the Manarkad region of the Kottayam district.

LCMS analysis of sample: Using Phenomonex Phase C-18 columns (25 cm x 2.5 mm) and an 80:20 water:acetonitrile ratio, the leaf extract was separated chromatographically at a temperature of 25 oC and a flow rate of 1.5 ml/min. The 50–1000 m/z range of the electronic spray ionization method was employed. Using an in-house mass spectral library made of pure substances and comparing the mass spectrum data to Wiley 275, the isolated ingredients were identified using Class V P integrated software.[61]

Extraction of papaya: Smaller chunks of young papaya leaves were triturated in a mortar with a little water. To extract the leaf juice, the resultant extract was filtered.[62]

Methodology:

The papaya grading method involves a number of steps, such as obtaining and gathering weight and picture data, pre-processing for image enhancement and segmentation, analyzing images to extract shape features, and classifying papaya sizes.[63]

Polygonum:

Lady's Thumb, or Polygonum persicaria Linn., is a blooming herbaceous plant in the Polygonaceae family. This tall perennial herb grows in the north of India (Punjab, Kashmir, Sikkim, and Himmalyan Region), England, southern Scotland, Europe, central Asia, and north of the Rockies in North America. It thrives in moist, shaded areas on higher elevation. It blossoms in June and May. The root stock can be divided to multiply the plant. The rhizome contains 21% tannin, which gives it a pronounced astringent flavor despite its odorlessness. Antinutritional compounds such alkaloids, saponins, tannins, and glycosides are what give food its bitter flavor [64].

Figure-1 Whole *Polygonum multiflorum* plant (A); The roots of *Polygonum multiflorum* (B); the roots of *Polygonum multiflorum* Praeparata (C).

Plant material:

The undersigned recognized the fresh polygonum persicaria plant material at the University of Kashmir's Department of Botany's Centre for Biodiversity and Taxonomy after it was collected from Lethpora, Pampora Kashmir, close to the Jhelum River. accompanied by Herbarium No. 2925 (KASH) voucher specimen.A grinding mill was then used to reduce the dried plant parts to a coarse powder.

Preparation of aqueous extract:

For 72 hours, the 500 g of generated powder was macerated in 1000 cc of distilled water. After filtering, the filtrate was dried in Petri dishes and heated to 40ºC until all of the water had

evaporated, concentrating it into a dark green residue.

Biochemical analysis:

The rats were put to sleep with ether, and blood samples were taken using the retro-oribital puncture technique and placed in tubes for biochemical analysis. To separate the serum, blood samples were centrifuged for ten minutes at 3000 rpm. After the animals' blood was collected, they were killed under ether anesthesia, and the liver tissue was taken out and subjected to established protocols for biochemical examination [65].

Histopathology:

After the experiment, the animals were beheaded, and the liver was quickly removed, cut, and cleaned with saline. The liver tissues were embedded in paraffin wax and stored with 10% formalin. Sections ranging in thickness from 4 to 5 microns were cut using a rotating microtome. After preparation, the liver portions were encased in paraffin wax. Photomicrographs were taken for histological analysis after sections were cut and stained with eosin and hematoxylin[66]. Several study animals' livers were promptly stored in a 10% buffered neutral formalin solution when the investigation was completed. Following fixation, the tissues were embedded in paraffin, serial slices were cut, and hematoxylin and eosin stain was applied. A light microscope was used to examine the slides, and pictures were obtained [67].

Reference:

1. Maqbool, M., Rasool, S., Dar, M. A., Bashir, R., & Khan, M. (2019). Hepatotoxicity and Hepatoprotective agents: A Mini review. PharmaTutor, 7(9), 34-40.
2. Shirani, M., Raeisi, R., Heidari-Soureshjani, S., Asadi-Samani, M., & Luther, T. (2017). A review for discovering hepatoprotective herbal drugs with least side effects on kidney. Journal of nephropharmacology, 6(2), 38-48.
3. Zeashan, H., Amresh, G., Singh, S., & Rao, C. V. (2008). Hepatoprotective activity of Amaranthus spinosus in experimental animals. Food and Chemical Toxicology, 46(11), 3417-3421.
4. Delgado-Montemayor, C., Cordero-Pérez, P., Torres-González, L., Salazar-Cavazos, M. D. L. L., Saucedo, A. L., Paniagua-Vega, D., & Waksman-Minsky, N. H. (2022). Development of a hepatoprotective herbal drug from turneradiffusa. Evidence-Based Complementary and Alternative Medicine, 2022.
5. Kumar, A. (2012). A review on hepatoprotective herbal drugs. Int J Res Pharm Chem, 2(1), 96-102.
6. Delgado-Montemayor, C., Cordero-Pérez, P., Salazar-Aranda, R., & Waksman-Minsky, N. (2015). Models of hepatoprotective activity assessment. Medicinauniversitaria, 17(69), 222-228.
7. Farghali, H., Kemelo, M. K., Wojnarová, L., &Canová, N. K. (2016). In vitro and in vivo experimental hepatotoxic models in liver research: applications to the assessment of potential hepatoprotective drugs. Physiological research, 65.
8. Wang, X., Wu, Q., Liu, A., Anadón, A., Rodríguez, J. L., Martínez-Larrañaga, M. R., ... & Martínez, M. A. (2017). Paracetamol: overdose-induced oxidative stress toxicity, metabolism, and protective effects of various compounds in vivo and in vitro. Drug metabolism reviews, 49(4), 395-437.
9. Dass, E. (2020). A brief review on Drug-induced hepatotoxicity: Use of hepatoprotective agents. IP Int J Comprehensive Adv Pharmacol, 5(1), 14-8.
10. Bhardwaj, A., Khatri, P., Soni, M. L., & Ali, D. J. (2011). Potent herbal hepatoprotective drugs-A review. Journal of Advanced Scientific Research, 2(02), 15-20.
11. Ai, G., Liu, Q., Hua, W., Huang, Z., & Wang, D. (2013). Hepatoprotective evaluation of the total flavonoids extracted from flowers of Abelmoschus manihot (L.) Medic: in vitro and in vivo studies. Journal of Ethnopharmacology, 146(3), 794-802.
12. Ahmad, F., & Tabassum, N. (2012). Experimental models used for the study of antihepatotoxic agents. Journal of Acute Disease, 1(2), 85-89.
13. Delgado-Montemayor, C., Cordero-Pérez, P., Salazar-Aranda, R., & Waksman-Minsky, N. (2015). Models of hepatoprotective activity assessment. Medicinauniversitaria, 17(69), 222-228.
14. Kumar, A., Susmitha, K., Swathy, B., Ramu, E., & Venkatesh, B. (2014). A review on liver disorders and screening models of hepatoprotective agents. Int J Allied Med Sci Clin Res, 2, 136-150.
15. Varsha Kashaw, V. K., Nema, A. K., & Abhinav Agarwal, A. A. (2011). Hepatoprotective prospective of herbal drugs and their vesicular carriers-a review.
16. Patil, B. R., Bamane, S. H., &Khadsare, U. R. (2011). In vitro protection of hepatocytes

by Alocasia macrorrhiza leaf juice against CCl4 and tylenol mediated hepatic injury. Int J Pharm Appl, 2(2), 122-127.
17. Vodovotz, Y., Kim, P. K., Bagci, E. Z., Ermentrout, G. B., Chow, C. C., Bahar, I., & Billiar, T. R. (2004). Inflammatory modulation of hepatocyte apoptosis by nitric oxide: in vivo, in vitro, and in silico studies. Current molecular medicine, 4(7), 753-762.
18. Olinga, P., & Schuppan, D. (2013). Precision-cut liver slices: a tool to model the liver ex vivo. Journal of hepatology, 58(6), 1252-1253.
19. Gandolfi, A. J., Wijeweera, J., & Brendel, K. (1996). Use of precision-cut liver slices as an in vitro tool for evaluating liver function. Toxicologic pathology, 24(1), 58-61.
20. Guillouzo, A. (1998). Liver cell models in in vitro toxicology. Environmental health perspectives, 106(suppl 2), 511-532.
21. Van de Bovenkamp, M., Groothuis, G. M. M., Meijer, D. K. F., & Olinga, P. (2007). Liver fibrosis in vitro: cell culture models and precision-cut liver slices. Toxicology in vitro, 21(4), 545-557.
22. Natanzi, A. E., Ghahremani, M. H., Monsef-Esfahani, H. R., Minaei, B., Nazarian, H., &Sabzevari, O. (2009). An experimental model for study of the hepatoprotective activity of Nasturtium officinale (Watercress) against acetaminophen toxicity using in situ rat liver system. European Journal of Scientific Research, 38(4), 556-564.
23. Roth, R. A., & Ganey, P. E. (2010). Intrinsic versus idiosyncratic drug-induced hepatotoxicity—two villains or one?. Journal of Pharmacology and Experimental Therapeutics, 332(3), 692-697.
24. Russmann, S., Kullak-Ublick, G. A., &Grattagliano, I. (2009). Current concepts of mechanisms in drug-induced hepatotoxicity. Current medicinal chemistry, 16(23), 3041-3053.
25. Ahmad, F., & Tabassum, N. (2012). Experimental models used for the study of antihepatotoxic agents. Journal of Acute Disease, 1(2), 85-89.
26. Raj, V. P., Chandrasekhar, R. H., Vijayan, P., Dhanaraj, S. A., Rao, M. C., Rao, V. J., & Nitesh, K. (2010). In vitro and in vivo hepatoprotective effects of the total alkaloid fraction of Hygrophila auriculata leaves. Indian journal of pharmacology, 42(2), 99-104.
27. Zhou, G., Chen, Y., Liu, S., Yao, X., & Wang, Y. (2013). In vitro and in vivo hepatoprotective and antioxidant activity of ethanolic extract from Meconopsis integrifolia (Maxim.) Franch. Journal of Ethnopharmacology, 148(2), 664-670.
28. Shailajan, S., Joshi, M., & Tiwari, B. (2014). Hepatoprotective activity of Parmeliaperlata (Huds.) Ach. against CCl4 induced liver toxicity in Albino Wistar rats. Journal of Applied Pharmaceutical Science, 4(2), 070-074.
29. Jaeschke, H., Gores, G. J., Cederbaum, A. I., Hinson, J. A., Pessayre, D., &Lemasters, J. J. (2002). Mechanisms of hepatotoxicity. Toxicological sciences, 65(2), 166-176.
30. Simeonova, R., Kondeva-Burdina, M., Vitcheva, V., &Mitcheva, M. (2014). Some in vitro/in vivo chemically-induced experimental models of liver oxidative stress in rats. BioMed research international, 2014.
31. Roy, S. D., Das, S., Shil, D., & Dutta, K. N. (2012). Herbal hepatoprotective agents: A review. World J. Pharma. Res, 1(2), 87-99.
32. Saisho, D., & Takeda, K. (2011). Barley: emergence as a new research material of crop science. Plant and cell physiology, 52(5), 724-727.
33. Suman, D., & Sreeja, V. (2019). Barley: A cereal with potential for development of functional fermented foods. International Journal of Fermented Foods, 8(1), 1-13.
34. Zheng, Q., Wang, Z., Xiong, F., Song, Y., & Zhang, G. (2023). Effect of pearling on nutritional value of highland barley flour and processing characteristics of noodles. Food Chemistry: X, 17, 100596.
35. Jan, S., Khan, M. N., Jan, S., Zaffar, A., Rashid, R., Khan, M. A., ... & Mir, R. R. (2022). Trait phenotyping and molecular marker characterization of barley (Hordeum vulgare L.) germplasm from Western Himalayas. Genetic Resources and Crop Evolution, 69(2), 661-676.
36. Kolli, V. S., Garg, S., &Shirkole, S. S. (2023). Silos and bins. In Transporting Operations of Food Materials Within Food Factories (pp. 61-93). Woodhead Publishing.
37. Flavin, S., Meltonville, M., Taverner, C., Reid, J., Lawrence, S., Belloch-Molina, C., & Morrissey, J. (2023). Understanding early modern beer: An interdisciplinary case-study. The Historical Journal, 66(3), 516-549.
38. Biswas, S., & Ansari, M. J. (2023). Health-endorsing properties of cereal grains. In Cereal Grains (pp. 77-101). CRC Press.
39. Geng, L., Li, M., Zhang, G., & Ye, L. (2022). Barley: a potential cereal for producing healthy and functional foods. Food Quality and Safety, 6, fyac012.

40. Sidhu, J. S., Kabir, Y., & Huffman, F. G. (2007). Functional foods from cereal grains. International Journal of Food Properties, 10(2), 231-244.
41. Martínez Moreno, F. B., Igartua Arregui, E., & Solís Martel, I. (2017). Barley Types and varieties in Spain: a historical overview. Ciencia e InvestigaciónAgraria, 2017 (44 (1)), 12-23.
42. Malik, A. H. (2012). Governing grain protein concentration and composition in wheat and barley: use of genetic and environmental factors (Doctoral dissertation, Swedish University of Agricultural Sciences).
43. Fogarasi, A. L., Kun, S., Tankó, G., Stefanovits-Bányai, É., &Hegyesné-Vecseri, B. (2015). A comparative assessment of antioxidant properties, total phenolic content of einkorn, wheat, barley and their malts. Food Chemistry, 167, 1-6.
44. Son, B. K., Kim, J. Y., & Lee, S. S. (2008). Effect of adlay, buckwheat and barley on lipid metabolism and aorta histopathology in rats fed an obesogenic diet. Annals of Nutrition and Metabolism, 52(3), 181-187.
45. Malhotra, S. K. (2012). Fennel and fennel seed. In Handbook of herbs and spices (pp. 275-302). Woodhead Publishing.
46. Das, L., Raychaudhuri, U., & Chakraborty, R. (2013). Herbal fortification of bread with fennel seeds. Food Technology and Biotechnology, 51(3), 434-440.
47. Noreen, S., Tufail, T., Bader Ul Ain, H., Ali, A., Aadil, R. M., Nemat, A., & Manzoor, M. F. (2023). Antioxidant activity and phytochemical analysis of fennel seeds and flaxseed. Food science & nutrition, 11(3), 1309-1317.
48. Behera, S. K., Rath, A. K., & Sethy, P. K. (2021). Maturity status classification of papaya fruits based on machine learning and transfer learning approach. Information Processing in Agriculture, 8(2), 244-250.
49. Savakar, D. G., & Anami, B. S. (2015). Grading of bulk food grains and fruits using computer vision. Journal of Agricultural Engineering and Biotechnology, 3(1), 1.
50. Damez, J. L., &Clerjon, S. (2008). Meat quality assessment using biophysical methods related to meat structure. Meat science, 80(1), 132-149.
51. Magwaza, L. S., & Opara, U. L. (2015). Analytical methods for determination of sugars and sweetness of horticultural products—A review. Scientia Horticulturae, 184, 179-192.
52. Medina, J. D. L. C., Gutiérrez, G. V., & García, H. S. (2003). Pawpaw: post-harvest operation. Food andriculture Organization of The United Nations. 70p.
53. Marimuthu, S., &Roomi, S. M. M. (2017). Particle swarm optimized fuzzy model for the classification of banana ripeness. IEEE Sensors Journal, 17(15), 4903-4915.
54. Surya Prabha, D., & Satheesh Kumar, J. (2015). Assessment of banana fruit maturity by image processing technique. Journal of food science and technology, 52, 1316-1327.
55. Nandi, C. S., Tudu, B., & Koley, C. (2014). A machine vision-based maturity prediction system for sorting of harvested mangoes. IEEE Transactions on Instrumentation and measurement, 63(7), 1722-1730.
56. Saeed, O. M. B., Sankaran, S., Shariff, A. R. M., Shafri, H. Z. M., Ehsani, R., Alfatni, M. S., & Hazir, M. H. M. (2012). Classification of oil palm fresh fruit bunches based on their maturity using portable four-band sensor system. Computers and electronics in agriculture, 82, 55-60.
57. Liu, C., Liu, W., Lu, X., Ma, F., Chen, W., Yang, J., & Zheng, L. (2014). Application of multispectral imaging to determine quality attributes and ripeness stage in strawberry fruit. PloS one, 9(2), e87818.
58. Leekul, P., Chivapreecha, S., Phongcharoenpanich, C., &Krairiksh, M. (2016). Rician k-factors-based sensor for fruit classification by maturity stage. IEEE Sensors Journal, 16(17), 6559-6565.
59. Kaur, H., Sawhney, B. K., &Jawandha, S. K. (2018). Evaluation of plum fruit maturity by image processing techniques. Journal of food science and technology, 55, 3008-3015.
60. Workneh, T. S., Azene, M., & Tesfay, S. Z. (2012). A review on the integrated agro-technology of papaya fruit. African Journal of Biotechnology, 11(85), 15098-15110.
61. Akhila, S., & Vijayalakshmi, N. G. (2015). Phytochemical studies on Carica papaya leaf juice. International Journal of Pharmaceutical Sciences and Research, 6(2), 880.
62. Mukherjee, P. K. (2002). Quality control of herbal drugs: an approach to evaluation of botanicals. Business horizons.
63. Riyadi, S., Rahni, A. A. A., Mustafa, M. M., & Hussain, A. (2007, December). Shape characteristics analysis for papaya size classification. In 2007 5th Student Conference on Research and Development (pp. 1-5). IEEE.
64. Dar, M. S., Tahir, A., Sahu, D., & Mittal, D. K. (2020). HEPATOPROTECTIVE EFFECT

OF POLYGONUM PERSICARIA (LINN.) AQUEOUS EXTRACT ON CARBON TETRACHLORIDE INDUCED HEPATOTOXICITY IN ALBINO RATS. Journal of Advanced Scientific Research, 11(04), 43-47.

65. Pari, L., & Kumar, N. A. (2002). Hepatoprotective activity of Moringa oleifera on antitubercular drug-induced liver damage in rats. Journal of Medicinal Food, 5(3), 171-177.
66. COŞKUN, Ö. (2000). Antioxidant and hepatoprotective activity of vitamin E and EGb 761 in experimental endotoxemic rats. Turkish Journal of Medical Sciences, 30(5), 427-432.
67. Sreenivasamurthy, B., Banji, D., & Banji, O. (2012). Investigation on antioxidant and hepatoprotective activity of ethanolic leaf extract of Polygonum glabrum Wild on carbon tetrachloride-induced hepatotoxicity in rats. Spatula DD, 2, 199-205.