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Article

A Histological and Physiological Analysis to Assess The Protective Function Rats' Hepatotoxicity Caused by Acetaminophen is Inhibited by an Alcoholic Extract of Garden Cress Seeds (Lepidium Sativum)

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Abstract: To assess how well the alcoholic extract of Garden Cress (Lepidium sativum) protects against acetaminophen-induced hepatotoxicity by enhancing erythropoietin levels and other physiological indicators. Protein, dietary fiber, vitamins, minerals, and vital amino acids are all abundant in garden cress seeds. Additionally, they contain phytochemicals that have been shown to help decrease blood triglycerides and cholesterol as well as prevent and inhibit the formation of cancer. One of the most popular and extensively used analgesics and antipyretics in the world is acetaminophen. It is an appropriate drug for cress seed extract, which is crucial for shielding the liver from carbon tetrachloride (CCl-4) damage. A study using rats showed that adding 200–400 mg/kg of cress seed extract to their daily diet significantly reduced hepatotoxicity. The rats were split into three groups: a control group, a group that was treated to uronic acid, and a group that was subjected to Ccl-4 to cause liver injury. Despite this, the number of documented cases of liver damage brought on by excessive dosages of the medication has been steadily rising annually throughout the world.

Keywords: Garden Cress (Lepidium Sativum), Acetaminophen, Hepatotoxicity, Anti-Inflammatory, Antioxidant

Introduction

Due to their efficacy and safety, the use of medicinal plants for the prevention and treatment of common ailments has recently expanded widely and quickly [1]. Due to their abundance of active components and compounds, several of these plants are also utilized in the production of different medicinal substances. Garden cress (Lepidium sativum) is one such plant. Similar to non-steroidal anti-inflammatory medicines (NSAIDs), garden cress has anti-inflammatory, antioxidant, and antibacterial qualities in addition to functioning as a pain reliever and blood pressure reducer [2].

The activation of the cytochrome P450 pathway, mainly in the renal cortex; the drug's binding to prostaglandin endoperoxidase; the production of toxic metabolites in the renal medulla; the drug's deacetylation by N-deacetylase enzymes; and the production of dangerous free radicals, which

ultimately cause nephronesis, are some of the possible mechanisms of acetaminophen-induced nephrotoxicity [3].

The interstitial cells that surround the renal tubules create and release erythropoietin (EPO) through the activation of hypoxia-inducible factor (HIF), which regulates the metabolic response of many genes to hypoxia. The erythroid colony-forming unit (E-CFU) is likewise stimulated by EPO [4]. The activation of the cytochrome P450 pathway, mainly in the renal cortex; the drug's binding to prostaglandin endoperoxidase [5]; the production of toxic metabolites in the renal medulla; the drug's deacetylation by N-deacetylase enzymes; and the production of dangerous free radicals, which can cause nephrosis, are some possible mechanisms of acetaminophen-induced nephrotoxicity [6].

The inflammatory process that causes anemia includes oxidative stress, and the degree of oxidation is directly correlated with the inflammatory state. These processes include hepcidin synthesis, which restricts intestinal iron absorption and the mobilization of iron reserves by binding to ferropotin on the cell membrane, and damage to the structure of the red blood cell membrane, which results in a shorter lifespan [7], [8].

Aim of Study

To assess how well the alcoholic extract of Lepidium sativum seeds protects against acetaminophen-induced hepatotoxicity and nephrotoxicity by enhancing erythropoietin levels and other physiological parameters in rats.

2-1Medicinal Plants:

2-1-1 Lepidium sativum

Before spreading over the world, Lepidium sativum, a member of the Brassicaceae family, was recognized for ages in Eastern countries. Because of its volatile oils, it is well-known for having a strong scent. Numerous conditions, including bone fractures, inflammation, and muscle pain, are treated with these oils [9]. Lepidium sativum is also used to treat headaches, sore throats, coughs, and asthma. It is used to treat syphilis and is a diuretic. This plant is also used to boost immunity and relieve constipation in Europe [10]. Garden cress seeds are added to some meals because of its vital nutritional content, which includes proteins, dietary fiber, and omega-3 fatty acids [11].

2-1-2 General Description of Garden Cress (Lepidium sativum)

An annual herbaceous plant is garden cress. It can grow up to 60 cm tall and is curly, branched, and upright [12]. The leaves are 5–6 cm long and might be whole, pinnate, or lobed. The flowers are carried on tall stalks and are thick with pink or white petals. The pods are spherical, elliptical, dispersed, grooved at the top, broad or patterned, and winged [13].

2-1-3 Microscopic Characters of Lepidium sativum Seeds

Lepidium sativum seeds' microscopic features showed that the endosperm is made up of thick-walled, polygonal cells. The embryonic cells are tiny and polygonal, and the embryo appears as a deep structure encircled by endosperm cells [14].

2-1-4 Chemical and Nutritional Composition of Lepidium sativum Seeds

Significant levels of protein (24.2%), fat (23.2%), carbs (30.7%), fiber (11.9%), ash (7.1%), and moisture (2.9%) are seen in the approximate composition (%) of garden cress seeds. The plant species, the stage of seed collection, and the geological and climatic circumstances of the harvested region all affect this estimated composition [15]. When evaluating the nutritional value of plant fruits and seeds, this is a crucial component. While low moisture level indicates stability, quality, and longer shelf life, high ash content signifies that garden cress seeds are a valuable source of minerals. Garden cress seeds have a high nutritional value because of their high protein and fat content [16].

2-2: Antioxidant

Garden cress seeds have antioxidant properties because of tocopherol and other phenolic compounds. Tocopherol is a significant antioxidant that protects essential fatty acids and vitamin A from oxidation and aids in preventing tissue damage. Furthermore, it has been demonstrated that garden cress seed extract reduces oxidative stress and, consequently, the cytotoxicity that hydrogen peroxide induces in liver cells [17]. It also possesses therapeutic and kidney-protective properties by scavenging free radicals. The alcoholic extract of garden cress seeds maintains the homeostasis of enzymes such as Na+/K+ ATPase, Ca++ ATPase, and Mg ++ ATPase [18].

2-2-1: Anti-diabetic

It has been discovered that garden cress seeds' alkaloids can effectively lower elevated blood sugar levels. In people with non-insulin-dependent diabetic mellitus (NIDD), using garden cress seeds was linked to a 41% drop in starch hydrolysis and, as a result, a reduction in the blood glucose response [19].

2-2-2: Laxative Effect

The mucilaginous material found in garden cress seeds is made up of uronic acid and cellulose. Additionally, they contain polysaccharides that expand in the digestive tract when water is present [20]. Polyuranide chains with ionized carboxyl groups, which become wet and swelled in the presence of water, are the cause of this swelling. Consequently, when constipation strikes, garden cress seeds can be used as a laxative [21].

2-2-3: Hepatoprotective Benefits

Additionally, carbohydrates found in cress seeds expand when water is present in the digestive system. Polyuranide chains with ionized carboxyl groups, which become wet and swelled in the presence of water, are the cause of this swelling. Consequently, when constipation strikes, cress seeds can be used as a laxative [22].

2-2-4: Hepatoprotective Effects

Carbon tetrachloride (CCl-4) damage to the liver can be prevented with the use of cress seed extract. A previous study conducted on rats demonstrated a significant reduction in hepatotoxicity when 200-400 mg/kg of cress seed extract was mixed with their daily food [23]. The rats were split into three groups: a control group, a group given CCl-4 to cause liver damage, and a group given both CCl-4 and cress seed extract.After ten days, it was discovered that the group treated with CCl-4 had very high levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum bilirubin, while the group treated with cress seed extract had much lower levels of these variables [24]. Garden cress seeds have a preventive impact because they include flavonoids, tannins, alkaloids, coumarins, and terpenes, which boost the antioxidant effect and lessen the production of free radicals brought on by CCl_4, the primary cause of liver damage [25].

2-2-5: Protection against nephrotoxicity

The impact of garden cress seed extract on doxorubicin-induced nephrotoxicity (DXN) was investigated. Four groups of rats were created. When compared to the control group, the group receiving the medication alone showed a notable rise in blood creatinine and urea levels [26]. Blood creatinine and urea levels were significantly lower in the group treated with garden cress seed extract and the medication than in the group administered the medication alone [27]. Compared to the medication group, the group treated with the seed extract had normal urea and creatinine levels. Additionally, histological analysis revealed that garden cress seed extract considerably reduced doxorubicin-induced renal tubular necrosis [28].

2-3 :Acetaminophen

2-3-1: Chemical and Physical Properties of Acetaminophen

With a molecular weight of 151.16 g/mol, a melting point of 169–170°C, a pH of 5.3–6.5 at 25°C, and a density of 1.293 g/cc, acetaminophen is a widely used medication. The formula for its molecules is $C_2H_2NO_2$ [29]. Water, ethanol, acetone, chloroform, glycerol, methanol, and alkaline hydroxide solutions can all dissolve this white, odorless crystalline powder. It is insoluble in pentone, benzene, and diethyl ether but somewhat soluble in ether [30].

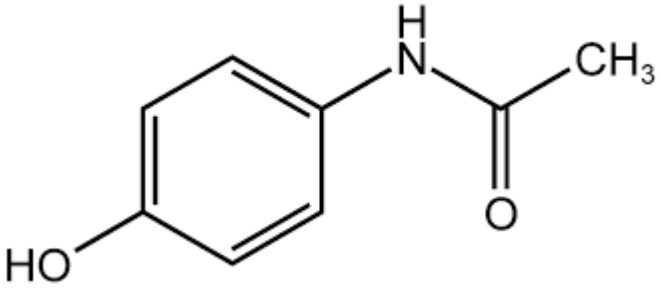

Figure 1. Shows the structural formula of the drug.

2-3-2: Mechanism of Action of Acetaminophen

Unlike non-steroidal anti-inflammatory medicines (NSAIDs), acetaminophen acts as an analgesic and antipyretic by preventing cyclooxygenase (COX) enzymes from producing prostaglandins. Acetaminophen has been shown to have no effect on tissue inflammation [31]. This has been explained by the fact that the enzyme known as cyclooxygenase or prostaglandin H2 synthetase (PGHS), which metabolizes arachidonic acid to prostanoids, such as prostaglandins and thromboxanes, has two active sites: COX and peroxidase (POX) [32]. The two-step process of converting arachidonic acid to prostanoids involves activity at the COX site to form hydroperoxide, which is unstable. Prostaglandin HBr (PGH2) is then produced via the Pox site [33]. Cox's enzymatic activity is contingent upon its oxidized state. In healthy cells, acetaminophen indirectly inhibits the oxidized form of Cox at the Pox site when arachidonic acid levels are low [34]. Acetaminophen is a strong inhibitor of PG production because it stops Pox from regenerating physiologically. Hydroperoxide levels are elevated and prostaglandin production is only marginally reduced in infected cells [35]. In contrast to NSAIDs, which operate on both Cox-1 and Cox-2, Cox-1 was believed to be active in the central nervous system rather than at the site of tissue damage or inflammation. Consequently, acetaminophen inhibition has very potent analgesic and antipyretic effects but no anti-inflammatory efficacy [36].

2-3-3: Metabolism and Secretion Acetaminophen Metabolism and Excretion

Three significant routes have been identified in the liver's critical role in the metabolism of acetaminophen [37]. About 55–60% of the metabolism of acetaminophen is attributed to glucuronide, 20–30% to sulfur, and less than 15% to N-hydroxylation, dehydration, and glutathione conjugation processes. Hepatic cytochrome P450 is the main enzyme involved in the drug's metabolism, which results in the alkylating products N-acetyl-benzoquinone imine (NAPBQI), also referred to as N-acetylimidoquinone [38]. These reactions specifically include the enzymes CYP450, CYP2E1, and CYP3A4. Inactive metabolites are produced by all three processes. The kidneys eliminate non-toxic NAPBQI from the body [39]. After taking the medication, patients' urine has been shown to include glucuronide, sulfate, mercaptorate, conjugated cysteine, and free acetaminophen [40].

2-4: Effect of Alcoholic Extract of Cress Seeds and Acetaminophen on Liver Tissue

Male rats in the control group had normal liver tissue when examined under a microscope. The hepatocytes' cytoplasmic and nucleolar components seemed normal, and there was no dilatation, bleeding, or congestion in the liver lobe's principal veins [41]. Additionally, the hepatic cords and hepatocytes were normal, and the interstitial connective tissue showed no signs of edema, inflammatory cell infiltration, or necrosis. On the other hand, histological analysis of the livers of male rats given a 1000 mg/kg acetaminophen injection showed a number of pathological effects, such as cytoplasmic destruction of hepatocytes, dilatation of some central veins and damage to others, congestion and hemorrhage, and destruction of the interstitial connective tissue of the liver, along with the appearance of hemorrhages and infiltrations [42]. When liver tissue from male rats that had been orally injected with a 250 mg/kg alcoholic extract of garden cress seeds and acetaminophen was examined, a number of aberrant alterations were seen, such as hemorrhages in the interstitial connective tissue of the liver and in some central veins, as well as dilatation of other veins. In contrast to the aforementioned, histological analysis of liver sections from males given acetaminophen and a 300 mg/kg alcoholic extract of garden cress seeds orally revealed no appreciable pathological alterations [43]. The normal appearance of the cellular structures confirmed the protective function of garden cress's chemical components at this concentration (300 mg/kg) in lessening the drug's harmful effects [44]. Additionally, microscopic analysis of histological sections from the livers of males in the group given only a 250 mg/kg alcoholic extract of garden cress seeds and those given the same extract at a dosage of only 300 mg/kg revealed no discernible abnormalities [45].

2-4-1: Chemical Analysis of the Alcoholic Extract of Cress Seeds Using GC-MS

The alcoholic extract of cress seeds included eighteen different chemical constituents, according to the current study's findings. These findings were in line with other research [46] that verified the existence of oleic acid and octanol, which was also reported in the present investigation. The findings, however, conflicted with those of other investigations [47], which found 46 chemicals. This discrepancy could be caused by extraction techniques, length of extraction, ambient factors, harvesting time of cress

seeds, plant growing season, kind of seed, or solvents. Variations in the chemical compounds found in the plants could have resulted from all of these variables [48].

2 -4-2 :Effect of Treatment with Alcoholic Extract of Cress Seeds and Acetaminophen on Body Weight and Rate of Weight Change in Male Rats

The current study's findings showed that the acetaminophen-treated group's body weight significantly decreased. These findings aligned with some research [49], but not with others. This could be explained by the fact that certain studies have shown that using high-dose acetaminophen for 60 days may have resulted in a number of gastrointestinal problems, including nausea and appetite loss (50). Alternatively, it can be because of the adverse effects of the medication, which could have adversely impacted the brain's satiety and appetite centers, resulting in a notable reduction in body weight. Under the negative effects of the medication, the weight loss could be explained by an increase in catabolic processes relative to anabolic activities [50]. As seen in the experimental animals given acetaminophen, this causes the animals to consume stored body fat, which results in weakness, lethargy, and decreased activity. Additionally, the medication negatively impacted the kidney tissue of the animals receiving treatment, which led to a reduction in feed intake and consequent substantial weight loss [51]. The medication specifically damaged the thyroid gland, leading to hyperthyroidism, which is characterized by high serum thyroid hormone levels and a consequent marked reduction in body weight [52]. There was no discernible difference in body weight between the 500 mg/kg + acetaminophen-treated group and the control group. This could be explained by the active chemical substances found in garden cress seeds, namely flavonoids, which have antioxidant properties. Alternatively, it might be because garden cress seeds contain a variety of amino acids and vitamins, including C and A, which make garden cress seed extract a chemopreventive agent. These substances aid in maintaining body weight by greatly boosting the body's immunity against illnesses [53]. However, there was no discernible difference in body weight between the group that received oral treatment with the alcoholic extract of garden cress seeds at 250 mg/kg and 500 mg/kg and the control group. This could be because garden cress seeds contain a variety of fatty acids, amino acids, phenols, carotenoids, and other substances that may have preserved the digestive system's healthy operation and improved body weight maintenance [54].

2-4-3 Effect of Treatment with Alcoholic Extract of Cress Seeds and Acetaminophen on the Relative Weights of Liver and Kidneys in Male Rats

The liver weights of the acetaminophen-treated group were significantly lower than those of the control group in the prior trial. This runs counter to some research [55], which found that giving animals acetaminophen did not significantly alter their liver weight. The liver weights of the acetaminophen-treated group were significantly lower than those of the control group in the prior trial. This runs counter to certain research [56], This verified that giving mice acetaminophen had no appreciable effect on their liver weight. The substantial drop in liver weight may have resulted from the histological consequences found in sections of the rats' livers in this group, such as clefting and fibrosis within the liver's interstitial connective tissue and dilatation of some major veins. Alternatively, the dosage may have produced hepatotoxicity by creating N-(acetyl-p benzoquinone imine) (NAPQI), a hazardous receptor that causes liver necrosis in experimental animals [57], causing the relative liver weights to decline. Rats' relative liver weights in the group administered 250 mg/kg of garden cress seed extract in addition to the medication significantly decreased as compared to the control group [58]. There was no discernible difference in liver weights between the group that received 500 mg/kg of garden cress seed alcoholic extract plus acetaminophen and the control group. This could be explained by the phenolic chemicals found in garden cress seeds, which shield the body's vital fatty acids and vitamin A. Acetaminophen is thought to lessen oxidative stress and shield bodily tissues from harm [59], or that the extract from garden cress seeds decreased oxidative stress, preventing or lessening the drug's cytotoxicity in liver cells. Additionally, there were no appreciable variations in liver weight between the 250 mg/kg and 500 mg/kg alcoholic extracts of garden cress seeds and the control group. The extract's carotenoids and tocopherols, which have anti-inflammatory and antioxidant properties and are very successful in shielding liver tissue from medication toxicity, may help to explain this [60].

2-4-4 : Histological Study

2-4-4-1 Effect of Alcoholic Extract of Cress Seeds and Acetaminophen on Liver Tissue

The cytoplasmic and nucleolar components of the hepatocytes appeared normal, the central veins of the liver lobe did not exhibit dilation, hemorrhage, or congestion, and the interstitial connective tissue did not suffer from edema, infiltration of inflammatory cells, or fibrosis, in addition to the regularity of the sinuses and hepatic bands, according to a microscopic examination of the liver tissues of male rats from the control group [61].

On the other hand, histological analysis of the livers of male rats given a dose of 1000 mg/kg of acetaminophen showed a number of pathological effects, such as cytoplasmic disintegration of the hepatocytes, dilatation of some central veins and damage to others, congestion and bleeding, as well as necrosis of the interstitial connective tissue of the liver and the appearance of bleeding [62]. Male rats' liver tissue that had been orally injected with an alcoholic extract of garden cress seeds and acetaminophen revealed a number of anomalies, including hemorrhages in the interstitial connective tissue of the liver and in certain central veins, as well as dilatation of other veins [63]. The examination of the histological sections of the livers of males who were administered orally the alcoholic extract of garden cress seeds at a concentration of 50 mg/kg + acetaminophen, in contrast to what was previously mentioned, did not reveal any significant pathological change because the cellular structures were normal. This confirms the protective action of the chemical components of the garden cress extract at a concentration of 50 mg/kg in preventing the toxic effects of the drug used in the previous study [64]. Additionally, upon microscopic inspection, the histological sections of the livers of the males in the group administered simply the 50 mg/kg alcoholic extract of garden cress seeds and those administered the same extract at a concentration of 100 mg/kg revealed no notable abnormalities. On the other hand, no notable pathological alterations were found in the histological sections of the livers of males who were orally administered the 500 mg/kg alcoholic extract of garden cress seeds plus acetaminophen [65]. The cellular structures were normal, indicating that the chemical components of the 500 mg/kg garden cress extract had a protective effect by preventing the harmful effects of the medication utilized in this investigation [66]. Additionally, there were no notable anomalies in the histological sections of the male livers in the group that received the 250 mg/kg alcoholic extract of garden cress seeds. Upon microscopic inspection, only the rats administered the identical extract at a dose of 500 mg/kg displayed no appreciable aberrant alterations [67].

Conclusions

When combined with acetaminophen, the alcoholic extract of garden cress seeds showed a protective effect, demonstrating the effectiveness of the plant's chemical components. particularly when the extract is utilized in high doses. In terms of protective efficacy, the 500 mg/kg concentration of the alcoholic extract of garden cress seeds outperformed the 250 mg/kg concentration of the same extract in all physiological and biochemical parameters. Additionally, compared to the control group, the 500 mg/kg concentration of the alcoholic extract of garden cress seeds increased antioxidant levels and, on the other hand, decreased oxidative stress markers. Additionally, it prevented acetaminophen-induced histological alterations in the kidneys and liver. Despite being a widely used analgesic, excessive and high doses of acetaminophen had detrimental effects on all the hematological, biochemical, and histological parameters investigated in this study.

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