Hepatoprotective effect of date seeds works through the antioxidant mechanism: a systematic review

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Abstract

Background: Most toxic substances in the body are metabolized in the liver, so it's giving a hepatotoxic effect. This review aimed to examine the effects of consumption of date seeds in liver protection.

Method: This research uses a systematic review design. Articles search is systematically carried out on the relevant publication databases such as Google Scholar, PubMed and DOAJ. The keywords used are "hepatoprotective", "date seed", and "date pits". Publication articles are limited between 2014 - 2019. All applicable studies were evaluated based on titles and abstracts, then continued to the content.

Results: we found 44 data sets of a total of 218 articles identified. Based on the inclusion criteria and critical assessment of the article, only 10 articles are in accordance with this review.

Conclusion: Date seeds contain antioxidants that significantly increase antioxidant activity, reduce free radicals and improve liver enzymes and tissues.

Keywords: hepatoprotective, SOD, SGPT, MDA, Interleukin

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Introduction

Many xenobiotic compounds in everyday life enter the body. These compounds are generally toxic and metabolized in the liver. Excessive toxicity can cause hepatotoxicity, thus developing into liver disease. Chronic liver disease is a cause of pain and death in the world. Xenobiotic compounds trigger free radicals that will cause oxidative stress and activate hepatic stellate cells, causing inflammation of the liver. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β contribute to increased liver damage(1). Several types of chemical compounds such as carbon tetrachloride and streptozotocin can oxidize liver cells so that damage occurs. Microorganism infections can also worsen the liver cell damage that arises. This process is accumulated and chronic so that the liver's performance decreases. Therefore it is necessary to increase liver cell repair by increasing immunity and stopping the chain oxidation reaction as a cause of liver damage. Chemical drugs can actually stimulate and increase liver damage because they need to be metabolized in the liver. Lately, herbal therapies have begun with minimal negative effects, including date seeds. Compounds contained in date seeds in the form of polyphenols and flavonoids are abundant, so it is thought to be able to repair and protect liver cells. The results of the phytochemical analysis show that date seeds extract contains a lot of flavonoids, tannins, reducing sugar, and anthraquinone glycoside(2–6).

Recently, research has shown that date seeds can work as antioxidants, anti-inflammatory, anti-cholesterol, anti-hyperglycaemic and immune-stimulant(7–12), but the hepatoprotective mechanism of date seeds has never been studied. Optimal use of date seeds has not been done, so it is necessary to study comprehensively the benefits of date seeds as hepatoprotective. Study of date seeds on hepatoprotective specifically with comprehensive indicator doesn’t conduct. This study aims to examine the mechanism of action of date seeds as hepatoprotective.
Methods

We selected datasets with comprehensive research published between 2014-2019 through the scientific databases in the form, PubMed, Google Scholar, and DOAJ. The positive terms that were used were "hepatoprotective" date pits”, and “date seed”. Search is done using the combination with Boolean operators ‘AND’, and ‘OR’. Details of the methods used are listed in Figure 1. The inclusion criteria are used for a systematic review of this study, original research, published in English, available full text, using experimental design and having control. The titles of the articles are considered to be important for the main point of review.

The initial literature search yielded 218 studies. After removing duplicates, 155 potential studies were evaluated. All papers are checked in 3 phases. The first phase, title, and abstract of the paper are checked using the inclusion criteria: using experimental design, there are controls, published in English as original articles and full text available. Of the total study of 155 titles, 44 met these inclusion criteria.

In the second phase, full-text articles are comprehensively reviewed. Studies that met exclusion criteria were excluded, namely no healthy control group, articles published without peer-reviewed, and no reports of inflammatory / oxidative marker data. Of the 44 studies, 10 articles did not meet the exclusion criteria so that they were available to be analyzed in depth (Figure 1). In the third phase, overlapping studies were issued, for example, the study had similarities.

1. Data extraction

A critical appraisal conducted on research that meets the inclusion criteria. Data is extracted independently from research that meets the criteria in the form of structured extraction data in the table (Table 1). The following data were extracted from each included study: aims, method, and results.

2. Data synthesis

The narrative results are summarized based on the findings from each study. A narrative synthesis is an approach in a systematic review carried out by reviewing findings in research relating to the review topic.
Results and Discussion

Many toxic compounds (drugs, pollution, chemicals) are often consumed by humans, for example, methotrexate, tamoxifen, flutamide, and others. This compound triggers the production of free radical species that will oxidize proteins, lipids and cell DNA, which can cause damage, especially liver cells. Laboratory results are often found to increase alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, gamma-glutamyl transpeptidase (GGT) and hypoalbuminemia (13). The body's antioxidant examination also showed a decrease in catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx), reduced glutathione (GSH) and increased MDA in CCl₄-induced mice. In hyperlipidaemic mice given atorvastatin, ALT and AST levels were lower with Ajwa seed extract consumption compared to those not given. This shows the ability of inner date palm extract to function as hepatoprotective (14). Consumption of a basal diet together with date seed powder can also reduce AST, GGT, and ALT. Based on biochemical analysis, DSP does not damage the organ but instead increases the body's antioxidant ability (15).

Provision of CCl₄ induction in mice causes an increase in free radicals resulting in liver and kidney damage. The results of the study show that giving dates can reduce levels of ALT, AST, LDH, ALP, GGT, MDA, LDL-C, bilirubin, creatinine, and increases of GSH, SOD, and GPX (16, 17). Some of these studies show that dates work as antioxidants to protect and repair liver cells due to exposure to free radicals (16).

Date seeds have been shown to play an anti-viral role and are thought to be related to their polyphenolic components, such as polysaccharides, lignin, and bioflavonoids (18). Many types of viruses are found to invade the liver causing chronic hepatitis, hepatic cirrhosis, liver failure, fibrosis and liver cell carcinoma (HCC). Continuous viral infections can cause liver damage due to the progressive accumulation of extracellular and collagen matrices. The results showed that dates were able to suppress activation of liver stellate cells and reduce pro-inflammatory cytokines TGF-β1 and angiogenic factors (VEGF, VEGFR-1, and CD31), so as to prevent the occurrence of liver fibrosis (1). Date palm works through antioxidant activity with a marked increase in antioxidant enzymes (SOD, GSH, GPx) and decreased lipid peroxidation products (malondialdehyde) in mice with liver cell carcinoma (19).

Giving date seeds for 14 days was also able to reduce inflammatory markers (IL-6, TNF-α, IL-1β, and CRP) and improve lymphocyte count in rats exposed to CCl₄. The liver enzyme examination results also showed a decrease in ALT levels after administration of date seeds in CCl₄-induced mice. This shows that dates can work as hepatoprotection (20). Dates have antioxidant, antibacterial, anti-obesity and antidiabetic activities (21).

In rats induced by heavy metals (Plumbum), administration of date seed extract can reduce MDA and nitrite, and increase GSH (22). This shows that date seeds are able to function as protection of the body against the toxicity of heavy metals. The mechanism that occurs shows that date seeds work as antioxidants. Rats were given 300 mg/kg of date seeds extract followed by exposure to heavy metals also showed a low increase in MDA compared to those who had not been given previous dates. This means that date seed extract can increase the body's antioxidant / protection before being exposed to free radicals from heavy metals.

In cases of diabetes mellitus induced by streptozotocin or alloxan, administration of this compound can cause toxic effects on the liver and kidneys. But the combination of giving insulin with date palm extract can minimize the risk of liver and kidney damage caused. This can be seen from the indicators of ALT, AST, γ-GT, BUN, albumin and creatinine levels as well as liver and kidney histological features (23, 24). Laboratory results in alloxan-induced mice showed that SOD, catalase, and GSH levels decreased, while MDA levels increased. Giving date seeds for 14 days can increase the levels of SOD, catalase, and GSH and reduce MDA levels (25, 26). This further strengthens the evidence that date seeds have a hepatoprotective effect through work as an antioxidant.

Toxic exposure of Azoxymethane in mice can reduce GSH levels and total antioxidant capacity (TAC), as well as increased lipid peroxidation and protein. Giving date seeds is also able to inhibit these free radical products. This is indicated by low levels of lipid peroxidation (MDA) and protein products, increased GSH and total antioxidant capacity (TAC) (27). In mice with liver damage due to gamma radiation, administration of date palm extract can also increase antioxidant enzymes and reduce liver damage indicator enzymes (28). The results of this study reinforce the argument that date seeds works as an antioxidant to protect the body from exposure to toxic substances (29). This is thought to be related to the components of date seeds that contain many flavonoids and phenolic compounds. Date palm activity is also related to the content of antioxidant compounds such as ascorbic acid, vitamin E, carotenoids, selenium, flavonoids, tannins and other phenolic compounds (30, 31).
Conclusion

Many dates contain polyphenol compounds and flavonoids. This compound has been shown to act as an antioxidant. The antioxidant activity of date seeds can protect liver cells from exposure to toxin-free radicals. Regular consumption of date seeds can reduce the risk of damage due to chronic exposure to toxic substances.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Author Contributions

SS and AP conceived, wrote, and revised the manuscript.

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References


Table 1. Comparative date seeds study as hepatoprotective agent

<table>
<thead>
<tr>
<th>No</th>
<th>Ref.</th>
<th>Aims</th>
<th>Method</th>
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<tr>
<td>1</td>
<td>(14)</td>
<td>To investigate the hypolipidemic and hepatoprotective potential of the commercially available crushed Ajwa date seed-extract on the toxicity caused by the atorvastatin in high-fat diet (HFD)-induced hyperlipidemic rats.</td>
<td>There were two main groups, Group I (normal control) and Group II (HFD); Group II was further divided into four subgroups: Group IIA (HFD control), Group IIB (Atorvastatin: A10)-6 rats were administered with 10 mg/kg atorvastatin daily for 30 days, Group IIC (Ajwa seed extract: AJ)-6 rats were given 1000 mg/kg Ajwa seed extract daily for 30 days, Group IID (AJ + A10)-6 rats were given Ajwa seed extract 1000 mg/kg and Atorvastatin 10 mg/kg daily for 30 days.</td>
<td>Ajwa seed extract lowered the serum cholesterol level in HFD rats and demonstrated the hepatoprotective effect in combination with atorvastatin by reducing the levels of ALT and AST. In conclusion, it protected the tissues from the detrimental effects of hyperglycermia and enhanced antioxidant activity. Furthermore, the dose-limiting toxicity of atorvastatin may be reduced if the Ajwa seed extract is incorporated in the current treatment regimens to treat hyperlipidemia in hypercholeremic individuals.</td>
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<td>2</td>
<td>(29).</td>
<td>To assess effects of date seeds and examines the oxidative stress status on serum and organs of Male Wistar rats after feeding them with basal diet comprising 0, 2, 4 or 8 g/kg date seed powder (DSP) for a period of 13 weeks.</td>
<td>Three date seed powder diets, DSP1, DSP2 and DSP3, were prepared by using 2 g/kg, 4 g/kg and 8 g/kg DSP in the diet, respectively. During the experimental period, the control group (5 rats) received the basal diet, and the DSP1, DSP2 and DSP3 groups (9 rats each) received the DSP1, DSP2 and DSP3 diets, respectively.</td>
<td>DSP suggestively (P &lt; 0.05) elevated the antioxidant defence system of the serum and organs. DSP decreased protein and lipid oxidative damages in the liver, muscle and brain. The consumption of DSP was associated with decreasing in the AST and GGT levels compared to the control group in a dose-dependent manner. A similar trend was observed for ALT, which was significant only in DSP1 and DSP3 compared to the control. DSP did not alter the organs’ function based on the analysis of biochemical markers. The results indicate that oxidative stress-related diseases could be possibly prevented by the DSP bioactive antioxidants.</td>
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<td>3</td>
<td>(16)</td>
<td>To evaluate the effect of a proanthocyanidin-rich extract of Khals date seeds in combating xenobiotic-induced hepatorenal injury via oxidative stress using in vivo models.</td>
<td>Five groups (I–V) of animals were used. Group I was kept as a normal control. Group II received CCl4 and served as a CCl4-intoxicated control. Groups III–V were assigned as treatment groups. Groups III and IV were pre-treated with DTX at doses of 50 and 100 mg/kg/rat orally, respectively; whereas groups V was pre-treated with silymarin (SYL) at 10 mg/kg/rat orally, for 17 days. Group I and II animals received a similar volume of vehicle once daily orally. At the 16th day, groups II–V received CCl4 in liquid paraffin (1:1) at a dose of 1.25 mL/kg/rat intraperitoneally.</td>
<td>Results of the histopathological examination and measurements of various hepatorenal serum indices and tissue biochemical markers demonstrated that DTX displayed marked protective potential against CCl4-induced liver and kidney injury at 100 mg/kg/rat. Relative to the control CCl4-intoxicated group, pre-treatment with DTX significantly (P &lt; .001) suppressed the elevated serum levels of ALT and AST, ALP, GGT, TC, LDL-C, bilirubin, creatinine, and calcium, whereas it significantly (P &lt; .001) increased the diminished serum levels of HDL-C and total protein (TP). Moreover, DTX significantly decreased MDA formation and increased TP synthesis in hepatorenal tissues compared with the intoxicated control. The improvement in biochemical parameters by DTX was observed in a dose-dependent manner and confirmed by restoration of normal histological features. The acute toxicity test of DTX in rats revealed safety of the extract. This study reveals that DTX enhances the recovery from xenobiotics-induced toxicity initiated by free radicals.</td>
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<td>4</td>
<td>(1)</td>
<td>To evaluate the antifibrotic effect of date flesh extract (DFE) or date pits extract (DPE) via inactivation of hepatic stellate cells (HSCs), reducing the levels of inflammatory cytokines including TNF-α, IL-6, and IL-1β. The increased levels of TGF-β1 and collagen deposition in injured liver were alleviated by both extracts. CCl4-induced expression of α-smooth muscle actin was suppressed indicating HSCs inactivation.</td>
<td>Coffee was used as reference hepatoprotective agent. Liver fibrosis was induced by injection of CCl4 (0.4 mL/kg) three times weekly for 8 weeks. DFE, DPE (6 mL/kg), coffee (300 mg/kg), and combination of coffee + DPE and coffee + DPE were given to CCl4-intoxicated rats daily for 8 weeks.</td>
<td>DPE, DPE, and their combination with coffee attenuated the elevated levels of inflammatory cytokines including TNF-α, IL-6, and IL-1β. The increased levels of TGF-β1 and collagen deposition in injured liver were alleviated by both extracts. CCl4-induced expression of α-smooth muscle actin was suppressed indicating HSCs inactivation.</td>
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To investigate the protective effect of Phoenix dactylifera L. seeds aqueous suspension against the chemically-induced hepatic injury in rats.

Liver injury was achieved by exposing Wistar rats to CCl$_4$ (10% in olive oil; 0.5 mL/rat; IP) twice a week for 4 weeks. Along with CCl$_4$, aqueous suspensions of raw or roasted Date seeds (1.0 g/kg) were administered orally in a daily manner.

To prove the decreasing of carbon tetrachloride toxicity using date seed (Phoenix dactylifera L.) steeping to improve rat immunity.

There were 6 groups of rat, healthy control (HC), negative control (NC), positive control (PC), treatment dose 1 g/kg (T1), treatment dose 3 g/kg (T3), and treatment dose 5 g/kg (T5). All of the groups were induced by CCl$_4$ before treatment except the HC group. The observed data were interleukin-6 (IL-6), lymphocyte count, and CRP.

To analyse its phenolics and flavonoids contents using HPLC – PDA as well as to investigate the protective properties of palm date extracts (fruit and seed) on liver functions in type 2 diabetic rats.

Rats were randomly divided into equal six groups (7 rats each); a) normal control (NC) group; normal rats, b) Diabetic control (DC) group; rats feed on high fat diet for 2 weeks, then received STZ (35 mg/kg) and received saline for 8 weeks c) DM + AFE group: as control group with aqueous Fruit extract (4 ml/kg BW) for 8 weeks, d) DM + MFE group: as control group with methanolic fruit extract (1mg/Kg BW) for 8 weeks, e) DM + AFE group: as control group with aqueous seed extract (10 ml/kg BW) for 8 weeks and f) DM + AFE group: as methanolic seed extract (2 mg/kg BW) aqueous seed extract.

To evaluate the anti-diabetic potential of the ethanolic extract of date palm seed in alloxan-induced diabetic rats.

There were five groups of rat. Group A was the control group, group B received date seed extract only (200 mg/kg bw) i.p, group C, D and E were the diabetic groups that received alloxan (150 mg/kg) and received saline for 8 weeks respectively; group C was the diabetic control group, group D and group E were treated with glibenclamide (5 mg/kg bw) and date palm seed extract (400 mg/kg bw) intraperitoneally for fourteen days.

Thirty-two male rats were divided into four groups of eight each as follows, Group A: untreated control; Group B: DEN control (180 mg/kg bw) intra peritoneally; Group C: DEN + ADE group; rats treated with ADE (Groups C, D) showed histological features of HCC and in rats treated with ADE (Groups C, D) partial to complete reversal of normal liver.
effects, and other beneficial properties of the aqueous extract of ajwa dates (ADE) in a rat model of diethylnitrosamine (DEN) induced liver cancer. Rats from all groups were assessed for liver cancer progression or inhibition by evaluating histological, biochemical, antioxidant enzyme status, cytokines and gene expression profiles.

Antioxidant enzymes such as SOD, GSH, GPx and CAT were increased, while the liver enzymes ALT, AST and ALP levels and lipid peroxidation were significantly decreased in Group C and Group D compared to Group B. Pro-inflammatory cytokines such as IL-1α, IL-1β, GM-CSF were increased in the serum of rats in Group B while the antitumor cytokines (IL-2, IL-12) were increased in ADE treated Groups (C, D). In addition, Alpha-Feto Protein (AFP) and IL-6 gene expression levels were upregulated in Group B, while they were significantly downregulated in ADE treated Groups (C, D).

10 (28). To evaluate the radioprotective efficacy of date pits extract (DPE) against γ-irradiation-induced liver damage in the male albino rats To calculate 30-day survival, median lethal dose of 30 days (LD50/30) and DRF, DPE was orally administered to rats for 21 days before irradiation with different doses (5, 6, 8, 10 and 12 Gy) of γ-rays and the rats were observed for 30 days post-irradiation. To evaluate the radioprotective efficacy of DPE against γ-irradiation induced-liver tissue damage, animals were divided into four groups (eight animals in each group). (i) Control: rats not subjected to any treatment; (ii) DPE: DPE was orally administrated (1000 mg/kg body weight) for 21 days; (iii) RAD: rats’ whole body exposed to 5 Gy of γ-rays; (iv) DPE + RAD: rats received DPE treatment for 21 days before γ-irradiation. Animals were sacrificed on the seventh day post-exposure to radiation.

The results showed that pre-treatment prior to irradiation with DPE resulted in a significantly higher 30-day survival rate of rats after exposure to different doses of γ-irradiation. Furthermore, DPE treatment improve the hepatic redox state significantly, manifested by increase of SOD and CAT activities and glutathione content associated with decrease of MDA level significantly. In addition, DPE exhibited hepatoprotective effect evidenced by increase in serum levels of insulin, testosterone, HDL-c and hepatic G6PHD activity associated with decrease in serum levels of AST, ALT, ALP, γ-glutamyl transferase (γ-GT), glucose, TC, TG, LDL-c and hepatic glucose 6 phosphatase (G6Pase) activity significantly, compared with irradiated group. Moreover, DPE showed positive modulation in the levels of hepatic metals (Fe, Zn, Cu and Mn).