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Journal of Natural Product and Plant Resources, 2018, 8 (3): 1-14
(http://www.scholarsresearchlibrary.com)

ISSN:2231-3184

Interactions between Acetaminophen and Phytotherapies: Overview for the Rational Use of Phytotherapics

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ABSTRACT

Paracetamol is the most used non-opioid analgesic in the world, and it is used to relieve mild to moderate pain. On the other hand, phytotherapy is the use of plants or herbal supplements with known pharmacological effects. It is common for patients to use phytotherapy in conjunction with conventional drugs. Drug interactions are pharmacological responses in which the effects of one or more medicinal products are altered by their joint administration. The objective of this study is to evaluate the interaction between phytotherapics and paracetamol when administered together. Methods: The protocol of this review was registered in the PROSPERO/ CRD42018100106 international database for systematic reviews. The research question for this study was: Is there an interaction between phytotherapics and paracetamol when given together? Six databases were screened: PubMed (Medline); Lilacs; Ibecs; BBO; Scielo; and Google Scholar, using the search strategy developed for PubMed (Medline). Results and Conclusion: Use of garlic, saffron, eucalyptus, Devil's Claw, pomegranate, ginger, celery, ginkgo, Kava-kava, salsa, and salgueiro could interfere with the effects of paracetamol, producing, for example, greater bleeding and liver failure, and putting the health of the patient at risk. However, the use of phytotherapy in combination with paracetamol has also shown benefits. For example, acetaminophen-induced oxidative damage can be alleviated by the use of some plants due to their antioxidant potential. Other plants have nephroprotective action and can inhibit the progression of hepatic injury. To promote the responsible use of phytotherapy, when used with conventional drugs, we must know the effects of this interaction.

Keywords: Drug interactions, Acetaminophen, Phytotherapy, Complementary alternative therapy.

INTRODUCTION

Analgesic drugs are divided into two groups according to their mechanism of action: non-opioids (used in the treatment of mild to moderate pain); and opioids (given in the treatment of more severe pain). Non-opioids act by inhibiting prostaglandin synthesis while opioids act on opioid receptors found in the central nervous system [1]. Acetaminophen, more commonly called paracetamol, is the most commonly used non-opioid analgesic in the world. Its mechanism of action is based on indirect receptor activation that is a complex of the neurotransmitter system related to several functions, including energy balance, emotional changes, pain, hyperthermia, and hyperphagia [2]. Despite being considered a drug with a good therapeutic and safe margin, paracetamol is responsible for triggering,

in high doses, acute liver failure, due to its hepatotoxicity. This phenomenon occurs because paracetamol is metabolized by CYP450 enzymes, forming NAPQI, a toxic metabolite [3].

Phytotherapy is a specialty of medical science using medicinal plants with known pharmacological effect to treat diseases and it can be used as an alternative or complementary treatment to conventional pharmacology treatment [4]. Use of herbal supplements in the world has increased dramatically in recent years. These products are not regulated by the Food and Drug Administration (FDA) with the same scrutiny as that given to conventional medicines. The use of herbal supplements in conjunction with conventional drugs can expose patients to possible drug interactions. [5] These interactions can be synergistic when the use of plants improve the action of the drug or antagonistic when interfering with the effect of conventional drugs that could put the health of the patient risk [6].

It is suggested that health professionals should be more aware of the possible adverse interactions between herbal supplements and analgesic drugs so as to avoid their possible interactions or to enhance the effects of conventional drugs. It is important, therefore, to create a rational and efficient phytotherapy. The creation of a rational and efficient phytotherapy is necessary with the aid of this system, especially with widely-used drugs such as acetaminophen [7]. According to the available information in the literature, this research aims to find possible interactions between paracetamol and phytotherapics.

MATERIALS AND METHODS

Information sources, eligibility criteria and search strategy

The protocol of this review was registered in the PROSPERO international database for systematic reviews (Register number: CRD42018100106). This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA Statement). The research question was: Is there an interaction between phytotherapics and paracetamol when given together?

The inclusion criteria were: clinical; in vitro; in vivo; in situ studies that evaluated the use of phytotherapics associated with paracetamol. The exclusion criteria include reviews; editorial letters; case reports; case series; studies published in a language other than English, Portuguese, or Spanish, and studies with no available full texts.

Six electronic databases were selected, including PubMed (Medline), Lilacs, Ibecs, BBO, Scielo, and Google Scholar. The search was undertaken in May 2018, using the search strategy developed for PubMed (Medline) (Table 1) and was adapted for other databases. The retrieved references were exported to the EndNote X7 software (Thompson Reuters, Philadelphia, PA, USA). Two authors independently assessed the Titles and Abstracts of all of the documents. After the removal of duplicates, the selection of the studies was performed in two phases. In phase 1, Titles/Abstracts that met the eligibility criteria were included. If a Title/Abstract provided insufficient information for a decision regarding inclusion/exclusion, the full text was obtained and evaluated in phase 2.

Table 1: Search strategy used in PubMed (MedLine).

	Search Terms
#3	Search #1 AND #2
#2	“Acetominophen” OR “Hydroxyacetanilide” OR “APAP” OR “p-Acetamidophenol” OR “p-Hydroxyacetanilide” OR “Paracetamol” OR “N-(4-Hydroxyphenyl)acetanilide” OR “Acetamidophenol” OR “N-Acetyl-p-aminophenol” OR “Acephen” OR “Acetaco” OR “Tylenol” “Anacin-3” OR “Anacin 3” OR “Anacin3” OR “Datril” OR “Panadol” OR “Acamol” OR “Algotropyl”
#1	“Herbal Therapy” OR “Herb Therapy” OR “phytotherapy”

Data extraction and items

The following data were extracted from the articles included in the literature review: author; type of study; vernacular names; preferred scientific name; and possible effect. If there was some information missing, the authors of the included papers were contacted via e-mail to retrieve any missing data.

RESULTS AND DISCUSSION

Use of medicinal plants is part of human culture. Herbal drug therapy is considered a common practice in traditional and alternative medicine and has been used since ancient times for the treatment of human diseases [8-10]. These

plants are usually easily accessible [11]. However, the possibility of drug interactions must be studied because plants can improve the action of the sintetic drug or be antagonistic in interfering with the effects of the sintetic drug in a way that could put the health of the patient at risk, especially with paracetamol, which is the most-used analgesic in the world. This research aims to find possible interactions between paracetamol and phytotherapics according to information from the available literature.

A total of 569 potentially relevant articles were identified from all of the databases. According to the PRISMA Statement, One hundred studies fulfilled all of the selection criteria and were included in the qualitative analysis.

A total of 22 of the included studies showed antagonistic effect or inhibition of acetaminophen when the phytotherapic was used with it. A total of 20 plant species were cited. These results are described in Table 2. The most cited effect was the inhibition of acetaminophen. The study in vitro model was used in 12 studies and the in vivo model was used in 10 studies.

Table 2: Phytotherapic with antagonic effect with paracetamol; ‡=inhibition,↑=increase and ↓=decrease; CT=carbon tetrachloride; SGOT=serum glutamate oxaloacetate transaminase; SGPT=serum glutamic pyruvic transaminase; LPO=lipid peroxidation; AO=Antioxidant activity; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; GSH/GSSG=reduced glutathione and oxidized glutathione, 4-HNE=4-hydroxynonenal; GGTP=gamma glutamyl transpeptidase; MPO=myeloperoxidase, NO=activity, nitric oxide; AA=acanthoic acid; GSH=hepatic glutathione; SOD =superoxide dismutase; CAT=catalase; GSH-Px =glutathione peroxidase; MDA=plasma creatinine, plasma and renal malondialdehyde; TB=total bilirubin; TP=total protein; 4-HNE=4-hydroxynonenal; P4502E1=CYP2E1Cytochrome; LD=lactate dehydrogenase; AOPP =renal advanced oxidation protein product; PPC=plasma protein carbonyl; LH=lipid hydroperoxides; GSTA2=glutathione S-transferase A2; Nqo1=quinone oxidoreductase1; Ho-1=heme oxygenase-1; Gclc=glutamate-cysteine ligases and MT=metallothionein; TBARS=thiobarbituric acid.

"Vernacular names"	Preferred Scientific Name	Possible efect	Type of study	Mechanims	Refs.
Açafrão	Curcuma longa	Internal bleeding	In vivo	‡ acetaminophen metabolism	[6]
Aipo	Apium graveolens	Unclear	In vivo	‡ coumarin 8-hydrolase	[18,19]
Salsa	Petroselinum sativum	Hepatoprotetor, Anticancerigeno	In vivo	↑ glutathione-S-transferase activity	[18,19]
Valerian	Valeriana officinalis	Inhibits paracetamol metabolism	In vitro	‡ Glucuronidation in vitro	[21]
Kava-kava	Piper methysticum	Liver toxicyti	In vivo	Unclear	[6,20,22]
Ocimum lamiifolium, Crassocephalum vitellinum, Guizotia scabra and Vernonia lasiopus	Rwandese herbal	Hepatotoxic	in vitro	↑ Dried metanol	[23]
Ginkgo	Ginkgo biloba	Internal bleeding	In vivo	↓ PAF	[6,22]
White Willow	Salix alba	Platelet inhibition	In vivo	Unclear	[22,24]
Garlic	Allium sativum	Inhibits paracetamol metabolism	In vivo	↓ PAF, adenosine, prostaglandins and thromboxanes	[25-27]
Cat´s claw	Uncaria tomentosa	Inhibits paracetamol metabolism	In vitro	‡ CYP3A4	[28]
Chamomile	Chamomilla recutita	Inhibits paracetamol metabolism	In vitro	‡ CYP3A4	[28,29]
Eucalyptus	Eucalyptus globulus	Inhibits paracetamol metabolism	In vitro	‡ CYP and CYP3A4	[30,31]
Clover, Red	Trifolium pratense	Inhibits paracetamol metabolism	In vitro	↓ 1A2, 2C8,2C9, 2C19, 2D6 and 3D4	[30]
Devil's claw	Harpagophytum procumbens	Inhibits paracetamol metabolism	In vitro	‡ CYP1A2, 2C8, 2C9, 2C19, 2D6 and CYP3A4	[30]

Peppermint, brandy mint, menthe poivree,	Mentha piperita	Inhibits paracetamol metabolism	In vitro	‡ CYP	[30]
Celandine, Greater Celandine,	Chelidonium majus	C. majus does not modify the hepatic effects of acetaminophen.	In vivo	No effect	[32]
Fennel	Foeniculum vulgare	Inhibits paracetamol metabolism	In vitro	‡ CYP3A4	[33,38]
Soy	Glycine max	Chemoprotector	In vivo	‡ P450	[34,31]
Bitter melon, papilla, bitter gourd, salsamino, corrila or karela	Momordica charantia	Inhibits paracetamol metabolism	In vivo	↓ CYP, CYP 3A4, 4A2 and ↑GST	[35]
Pomegranate	Punica granatum	Inhibits paracetamol metabolism	In vivo/ in vitro	↓ CYP3A and CYP1A2	[36]
Zingiber	Zingiber officinale	Inhibits paracetamol metabolism	In vitro	↓ CYP3A4	[37]
Keezhanelli or Kirunelli	Phyllanthus amarus	Inhibits paracetamol metabolism	In vivo/ in vitro	↓ P450, topoisomerase and CDC 2 kinase	[39]

The studies included that showed the synergistic effect of a phytotherapic with paracetamol are described in Table 3. A total of 88 studies were found with the potential to reduce or prevent the effects of acetaminophen. In these studies, 81 plant species were cited. The most cited synergistic effect was hepatoprotective activity, followed by a nephroprotective activity. The most used study model was in vivo, used in 97,7% of studies, with the in vitro model being used in only 3.3% of studies.

Table 3: Phytotherapic with synergistic effect with paracetamol; ‡=inhibition,↑=increase and ↓=decrease; CT=carbon tetrachloride; SGOT=serum glutamate oxaloacetate transaminase; SGPT=serum glutamic pyruvic transaminase; LPO=lipid peroxidation; AO=Antioxidant activity; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; GSH/GSSG=reduced glutathione and oxidized glutathione, 4-HNE=4-hydroxynonenal; GGTP=gamma glutamyl transpeptidase; MPO=myeloperoxidase, NO=activity, nitric oxide; AA=acanthoic acid; GSH=hepatic glutathione; SOD =superoxide dismutase; CAT=catalase; GSH-Px =glutathione peroxidase; MDA=plasma creatinine, plasma and renal malondialdehyde; TB=total bilirubin; TP=total protein; 4-HNE=4-hydroxynonenal; P4502E1=CYP2E1Cytochrome; LD=lactate dehydrogenase; AOPP =renal advanced oxidation protein product; PPC=plasma protein carbonyl; LH=lipid hydroperoxides; GSTA2=glutathione S-transferase A2; Nqo1=quinone oxidoreductase1; Ho-1=heme oxygenase-1; Gclc=glutamate-cysteine ligases and MT=metallothionein; TBARS=thiobarbituric acid.

"Vernacular names"	**Preferred Scientific Name**	**Possible efect**	**Type of study**	**Mechanisms**	Refs.
Sida indica	Abutilon indicum	Hepatoprotective activity	In vivo	↓ CT	[40]
Asparagus	Asparagus officinalis	Hepatoprotective activity	In vivo	↓ SGOT, SGPT, SALP, LPO	[41]
Phytotherapy anti-malária (AM1)	Phytotherapy anti-malária	Reduced the systemic availability	In vivo	AO	[42]
Eucalyptus	Eucalyptus globules	Alleviate the acetaminophen-induced damage	In vivo	↓ CAT, SOD, GSH-Px	[43]
Woolly-Leaved Fire-Brand Teak	Premna tomentosa	Alleviate the acetaminophen-induced damage	In vivo	AO	[44]
Old World forked fern	Dicranopteris linearis	Hepatoprotective activity	In vivo	↓ ALT, AST.	[45]
Sugarcane	Saccharum officinarum	Hepatoprotective activity	In vivo	AO	[46]

Curcumin	Curcuma longa	Hepatoprotective activity	In vivo	↓ Oxidative stress, ↑ GSH.	[47-49]
Lemon grass or oil grass	Cymbopogon citratus	Hepatoprotective activity	In vivo	↓ ALT, AST, ALP	[50]
Jaggery	Non-centrifugal cane sugar	Reduce renal damage	In vivo	AO	[51]
Asian pigeonwings,[1] bluebellvine, blue pea, butterfly pea, cordofan pea and Darwin pea	Clitoria ternatea	Hepatoprotective effect	In vitro	AO	[52]
Japanese alder	Alnus japonica	Hepatoprotective effect	In vitro	↓ LPO, SOD	[53]
Malayalam. Kilarannelli	Phyllanthus-polyphyllus	Hepatoprotective and antioxidant activity	In vivo	↓ AST, ALT, ALP, GGTP, LPO, SOD, GST	[54]
Amrul, Amboli, Chukatripati and others	Oxalis corniculata L	Hepatoprotective and antioxidant potential.	In vivo	AO	[55]
Berseem, berseem clover, Egyptian clover and others	Trifolium alexandrinum root	Nephroprotective activity	In vivo	↓ AST, ALT, ALP	[56]
Chandahar Tree, Cashmere Tree, Comb Teak or White Teak	Gmelina arborea	Hepatoprotective effects	In vivo	↓ SGOT, SGPT	[57]
Celery	Apium graveolens	Hepatoprotective effect	In vivo	↓ AST, ALT, ALP	[58]
Common Columbine, European columbine or others	Aquilegia vulgaris	Hepatoprotective effects	In vivo	AO	[59]
Skullcap	Scutellaria radix	Hepatoprotective effects	In vivo	↓ CYP2E1	[60]
Zingiber	Zingiber officinale	Nephroprotective activity	In vivo	↓ AST, ALT, ALP	[61]
Black Cumin	Nigella sativa	Hepatoprotective activity	In vivo	↓ GSH	[62]
Carqueja, bacanta, bacárida and others	Baccharis trimera	Hepatoprotective activity	In vivo	↓ AST, ALT	[63]
Stone Leaf, Akar mempelas putih	Tetracera loureiro	Hepatoprotective activity	In vitro/In vivo-Rats	↓ AST, ALT	[64]
Damask Rose	Rosa damascena Mill.	Hepatoprotective activity	In vivo	AO	[65]
Yellow Sweet Clover, kings-clover, sweet clover or sweet lucerne	Melilotus officinalis.	Hepatoprotective activity	In vivo	↓ SGOT, SGPT, ALP	[66]
Magnolia berry or five-flavor-fruit	Schisandra chinensis	Hepatoprotective activity	In vivo	AO	[67]
Russian Wormwood	Artemisia sacrorum Ledeb	Protective effects	In vivo	↓ AST, ALT	[68]
Coffee Senna, coffeeweed,	Cassia occidentalis	Hepatoprotective activity	In vivo	↑AST , ALT, SALP	[69]
Oval Leaf Pondweed, Oval Leaf Monochoria or Marshy betelvine	Monochoria vaginalis.	Nephroprotective activity	In vivo	AO	[70]
Oyster or pearl oyster mushroom	Pleurotus ostreatus	Nephroprotective activity	In vivo	↓ ALT, AST, GDH, creatinine, BUN, KIM-1and MDA; ↑ GSH, GSH-Px and SOD	[71]

Shingle tree	Acrocarpus fraxinifolius Arn	Hepatoprotective activity	In vivo	↓ALT, ALP, lipid profiles, TB and MDA; ↑ body weight, serum protein profile and AO	[72]
Propolis	Propolis	Hepatoprotective activity	In vivo	↓P4502E1, ↑GST, PST; ‡ phase I enzymes and induction of phase II enzymes	[73]
Black plum	Vitex doniana Sweet	Antioxidant properties and halted acetaminophen-mediated oxidative rout.	In vivo	↓levels of conjugated dienes, LH, MDA, PPC and fragmented DNA	[74]
Brown alga	Sargassum polycystum	Antilipemic property and Protect against acetaminophen-induced lipid peroxidation.	In vivo		[75]
Roselle	Hibiscus sabdariffa L	Mitigating paracetamol-induced hepatotoxicity.	In vivo	Ameliorating several indices of paracetamol toxicity	[76]
Cobbler's Tack	Glossogyne tenuifolia	Hepatoprotective activity	In vivo	↓ ALT, AST, GSH, GSSG; ↑GSH ; ‡ serum and LP	[77]
Sesame oil	Sesame oil	Hepatoprotective activity	In vivo	Reversed all APAP-altered parameters	[78]
Kutki	Picrorhiza	Hepatoprotective and hepatoregenerative.	In vivo		[79]
Halia	Zingiber officinale Roscoe	Hepatoprotective activity	In vivo	↓ AST, ALT, ALP, arginase and TB; ‡MDA	[80]
Blessed milk thistle	Silybum marianum	Hepatoregenerative effect	In vivo	Anti-aflatoxin activities	[81]
Wheel Cactus and opuntia cardona	Opuntia robusta and Opuntia streptacantha extracts	Hepatoprotective activity	In vivo	↓ LDH, cell necrosis, AST, ALT and ALP; ↑GSH and glycogen stores;	[82]
Gin Berry	Glycosmis arborea	Hepatoregenerative effect	In vivo	↓ SOD	[83]
Chirayita	Swertia chirata	Hepatoprotective activity	In vivo	AO	[84]
Black pigweed	Trianthema portulacastrum L.	Hepatoprotective activity	In vivo	↓ SGOT, SGPT, ALP, BRN; ↑ TP	[85]
Trachomitum venetum	Apocynum venetum	Hepatoprotective effects	In vivo	Scavenging free radicals, maintenance of cellular anti-oxidants levels and antioxidant enzymes activities. Suppressing cytochrome c release, caspase activation and DNA fragmentation.	[86]
Frank indigo	Indigofera tinctoria Linn	Hepatoprotective potential	In vivo	Reverse the altered parameters towards normal values.	[87]
Protium heptaphyllum	Protium heptaphyllum	Hepatoprotective potential	In vivo	↓ ALT , AST, histopathological alterations and replenished the GSH	[88]
Trade asas	Bridelia micrantha	Hepatoprotective activity	In vivo	↓ AST ,ALP, bilirubin; ↑ TP	[89]
Guava	Psidium guajava	Hepatoprotective activity.	In vivo	↓ AST, ALT ALP And bilirubin.	[90]
Sausage tree, Sodom apple, Roselle and Christmas bush	Kigelia africana, Hibiscus sabdariffa and Alchornea cordifolia	Hepatoprotective activity	In vivo	↓ NAPQI or scavenging ROS	[91]

Premna tomentosa	Premna tomentosa	Hepatoprotective potential	In vivo	Manteince of levels of LP products, GSH and mitochondrial enzymes (isocitrate dehydrogenase, α-keto glutarate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, NADH dehydrogenase and cytochrome-C-oxidase).	[92]
Frankincense,	Boswellia ovalifoliolata	Hepatoprotective potential	In vivo	↓ SGPT, SGOT, and LDH; ↑ GSH, CAT, SOD enzymes.	[93]
horse-radish tree	Moringa oleifera Lam.	Hepatoprotective potential	In vivo	↓ 4-HNE,MDA and liver marker enzymes	[94]
Korean Ginseng Root Extract	Korean red ginseng	Hepatoprotective activity	In vivo	↓ P450 2E1; ↑ GSTA2	[95]
Leafflower	Phyllanthus urinaria	Hepatoprotective activity	In vivo	↓P450 CYP2E1	[96]
Black cumin	Nigella sativa L.	Hepatoprotective activity	In vivo	↑serum creatinine, SOD, GSH; ↓ MDA	[97]
Curcumin	Curcuma longa	Hepatoprotective activity	In vivo	↓ MMP-8, reverse the altered genes expression of antioxidant and inflammatory cytokines.	[98]
Kulikhara	Asteracantha longifolia	Hepatoprotective activity	In vivo	↓enzymes, bilirubin, and lipids.	[99]
Apple of Sodom	Rhazya stricta	Hepatoprotective activity	In vivo	Improvement of the above liver function tests	[100]
Picroliv, Curcumim, Ellagic acid	Picrorhiza Kurroa, Curcuma longa, Ellagic acid	Hepatoprotective activity	In vivo	Reverse the altered parameters towards normal values.	[101]
Apple of Sodom, Sodom apple, stabragh, king's crown, rubber bush	Calotropis procera	Hepatoprotective activity	In vivo	Reverse the altered parameters towards normal values.	[102]
Common Columbine	Aquilegia vulgaris	Hepatoprotective activity	In vivo	↓ enzymatic, non-enzymatic and uninduced LPO; ↑ antioxidant enzymes	[103]
Treefern	Cyathea gigantea	Hepatoprotective activity	In vivo	↓ SGOT, SGPT, ALP, TB and also reversed the hepatic damage towards normal.	[104]
Downy Pepper	Piper puberulum	Hepatoprotective activity	In vivo	↓serum enzyme activities and ameliorated liver lesions. ↑ Nrf2, NAD(P)H, Nqo1, Ho-1, Gclc, MT	[105]
Roselle	Hibiscus sabdariffa L.	Hepatoprotective activity	In vivo	↓ LP, AAP-induced liver injury, pJNK, Bax and tBid; ↑ CAT, GSH	[106]
Black ginseng	Ginseng Radix nigra	Hepatoprotective activity	In vivo	↓ALT, AST, MDA, and Bax protein; ↑ Bcl-2	[107]
Phyllanthus Plant, Child Pick-a-back, Gulf Leafflower, Black Catnip,	Phyllanthus niruri	Hepatoprotective activity	In vivo	↓ GPT, ALP, LP, SOD, CAT, GST	[108]
Broom grass, broom weed, broomweed, cheese weed	Sida acuta Burm. f.	Hepatoprotective activity	In vivo	↓GPT, GOT, ALP and bilirubin.	[109]
Common tea or Tea plant	Thea sinensis melanin	Hepatoprotective activity	In vivo	↓ALT, TBARS, partial prevention of GSH depletion in the liver tissue.	[110]
Goldfinger plant	Echinophora platyloba	Hepatoprotective activity	In vivo	↓ ALT, AST, ALP, and MDA.	[111]

Moringa, drumstick tree	Moringa oleifera Lam.	Hepatoprotective activity	In vivo	↓ liver marker enzymes and the severity of the liver damage histologically.	[112]
Ben tree, wispy-needled yasar tree	Moringa peregrina l	Hepatoprotective activity	In vivo	↑GSH, CAT and SOD	[113]
Zingiber	Zingiber zerumbet rhizome	Nephroprotective activity	In vivo	↓ MDA, PPC, AOPP	[114]
Madras Leaf-Flower	Phyllanthus maderaspatensis	Hepatoprotective activity	In vivo	Prevented elevation of serum GPT, GOT and ALP.	[115]
Dandelion	Taraxacum officinale Weber	Hepatoprotective activity	In vivo	Scavenger activities against ROS and reactive nitrogen species	[116]
Epimedium koreanum	Acanthopanax koreanum Nakai	Nephroprotective activity	In vivo	↑ AST, ALT, GSH, SOD, CAT, GSH-Px activities, MDA l and ↓histopathological alterations	[117]
Bulkumia or Kumarialata	Smilax zeylanica L.	Hepatoprotective activity	In vivo	↓ ALT, ALP, TB; ↑ TP and albumin.	[118]
Common centaury or European centaury.	Centaurium erythraea L.	Nephroprotective activity	In vivo	↓ SGOT, SGPT, and LD	[119]
Bitter leaf	Vernonia amygdalina Del.	Hepatoprotective activity	In vivo	AO	[120]

Paracetamol is a drug with analgesic properties but is highly toxic to the liver. The daily dose should not exceed 4 g [12]. It is the most commonly used drug in self-medication [1]. Paracetamol is metabolized in the liver and its metabolism involves three main pathways: glucuronide conjugation; sulfate conjugation; and oxidation via the cytochrome P450 enzyme pathway. CYP2E1, CYP1A2, and CYP3A4 appear to be the isoenzymes of the cytochrome P450 system most involved in vivo. [13]. According to the pharmacokinetic profile of paracetamol, plasma concentrations reach a maximum of 0.5 to 1.0 h after administration of 500 mg or 1,000 mg paracetamol [14].

According to a US study [15], paracetamol is associated with more than 1,000,000 cases of poisoning, 56,000 visits to emergency departments, 26,000 hospitalizations, and 450 deaths per year [15]. The effects of acetaminophen overdosing may, however, be reduced by a well-established dose, which restores hepatic glutathione and thus avoids accumulation of NAPQI. In addition, it is suggested that inhibition of NAPQI formation may be useful in preventing acetaminophen overdose toxicity [16]. P450 (CYP) enzymes are particularly subject to phytotherapeutic interactions for induction or inhibition of their effect [17,18]. Any inhibitory effect of herbicidal residues on CYP may result in increased plasma and tissue concentrations that attain toxicity, while any inductive effect may cause a reduction in drug concentrations leading to decreased drug efficacy and treatment failure [18]. Interestingly, there are regional characteristics among populations, where individuals may have specific enzymes that may be more sensitive to phytotherapics [17].

Table 2 shows the relationship of plants interacting with paracetamol, especially via the cytochrome P450 pathway producing nephrotoxicity, particularly in long-term and high doses [6,18-39]. For example, when Curcuma longa (Açafrão) or Ginkgo biloba and paracetamol are together administered, this could result in an increase of internal bleeding, probably due to the increase in the inhibitory effect of acetaminophen on thromboxane production [6]. In the case of Kava-kava, used for anxiety, asthma, and depression, when administered with paracetamol it could cause liver problems like cirrhosis, hepatitis, and liver failure. Therefore, it is not advisable to manage them together [6,20]. Some widely-used plants in the population, like *Chamomilla recutita*, *Eucalyptus globulus*, and Garlic *Allium sativum*, inhibit paracetamol metabolism by mechanisms that are not fully understood [28-30]. All the above-mentioned examples serve as a caution in the use of some herbs when they are administered with conventional medicines, especially paracetamol. So, we should look for the best alternatives.

There are precedents establishing that the use of certain plants can have an antagonistic effect on paracetamol, which may put the patient's life at risk. However, the great majority of herbs used in phytotherapies have a positive and synergistic effect with respect to benefits of paracetamol. Table 3 shows that the best known beneficial effects of phytotherapeutics are hepatoprotective activity, renal protective activity, nephroprotective activity, and antioxidant effects. Some plants like Abutilon indicum, Clitoria ternatea, Alnus japonica, Gmelina arborea, and Apium graveolens have a hepatoprotective activity, and others like Ginseng, Radix nigra, Echinophora platyloba, and Smilax

zeylanica have a nephroprotective activity. Besides that, medicinal plants can cause reduction in side effects of nephrotoxicity and anticancer drugs via their antioxidant and anti-inflammatory properties [40-120]. These protective effects have been related to a variety of molecules found to be involved in the regulation of acetaminophen-induced oxidative stress, including c-Jun N-terminal kinase (JNK), tumor suppressor protein (p53), and nuclear factor erythroid 2-related factor (2Nrf2), which may serve as potential therapeutic targets for acetaminophen-induced acute liver injury. Other studies have referred to the protective role of plants through their antioxidant activity, such as that produced by Vernonia amygdalina, which, through this property, decreases the hepatic damage induced by paracetamol [120,121]. Antioxidant capacity of these natural products can be attributed to the levels of glutathione (GSH), superoxide dismutase, catalase, and other antioxidant enzymes. Those could also be attributed to the inhibition of acetaminophen metabolism or to a faster recovery from hepatotoxicity due to less injury being less. It is worth mentioning that, when compared with the current standard antidote N-acetyl cysteine, the herbal therapy cannot offer more outstanding therapeutic effects [122].

A hepatoprotective mechanism that is most described in the literature is one that is mediated by the significant modification of levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and glutamate dehydrogenase (GDH) [28]. One example of these hepatoprotective mechanisms is the use of *Pleurotus ostreatus*, which significantly reduces acetaminophen-induced elevated levels of ALT, AST, and GDH. In the anterior example, treatment with *Pleurotus ostreatus* significantly decreased acetaminophen-induced cell necrosis in liver and kidney tissues [30]. The decrease in AST levels as a protective effect has also been demonstrated in several studies that used different types of plants, such as *Glossogyne tenuifolia* [36], *Bridelia micrantha* [48]. All these mechanisms are fundamental in the main function that is described by phytotherapics; hepatoprotective activity.

CONCLUSION

Some herbs, like garlic, saffron, eucalyptus, Devil's Claw, pomegranate, ginger, celery, Ginkgo, Kava-kava, salsa, and salgueiro have been reported as being capable of interfering with the effects of paracetamol, producing, for example, greater bleeding and liver failure and putting the health of the patient at risk. The vast majority of herbs used have benefits, reducing the effects of paracetamol. Acetaminophen-induced oxidative damage can be reduced by the use of certain plants due to its antioxidant potential. Other plants have hepatoprotective effects, partially due to their anti-oxidant action, that can prevent renal damage, and many plants have nephroprotective action or can inhibit progression of hepatic injury. To promote responsible use of phytotherapy, when used with conventional drugs, it is important to know the effect of this resultant interaction. If the intention is to use medicinal plants as medicines, they must be previously validated where their action is proven and their potential toxicity is evaluated in the human species. As with any other medicine, this would promote their rationale.

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