



## Protective effects of broccoli sprout extract on Caspase 3 and liver function in female rats treated with methotrexate

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### Abstract

Methotrexate (MTX) is an analog of folic acid utilized as a low-dose treatment for autoimmune diseases, such as PsA or RA and a high-dose treatment for cancer. MTX increased the apoptosis by switching on caspase 3, which is switching on death protease, stimulating the specific incision of cellular proteinase. We chose BSE for this research because it content from glucoraphanin higher than adult broccoli, This research aimed to determine the levels of casp-3 and liver function to determinated protective effects of BSE in mitigating MTX impact in rat female due to lack of studies that addressed this matter especially in females which spread among them lots of autoimmune diseases requires MTX use RT-qPCR technique was used to determination levels of gene expression subsequent to RNA extraction. Our study suggested that BSE enhance liver functions and caspase 3 expression in rat that treated with MTX and broccoli sprout extract and in groups treated with BSE only if we compared it with control and MTX groups.

### Key words

Methotrexate(MTX), Broccoli sprout extract (BSE), cysteine-containing aspartic acid-specific proteases) CASP3 Alanine aminotranseferase(ALT), Aspartate aminotranseferase(AST), Alkaline phosphatase (ALP)

### Introduction

The liver is an important organ plays role in glucose metabolism and glycogen synthesis It also breaks poisons down into less dangerous substances, metabolizes drugs, and released bile and accumulated glycogen. Liver diseases produced because of Liver damage due to excessive alcohol intake, drug use and energy-rich foods that may result in severe sicknesses, like liver cancers and liver fibrosis which is progressing slowly and it

may be diagnosed in advanced stages [1]. Therefore routine testes for liver such as aspartate aminotransferase AST, and gamma-glutamyltransferase  $\gamma$ -GTP evaluation of alkaline phosphatase ALP and alanine aminotransferase ALT as enzymatic biomarkers are important to ensure liver health [2,3]. Methotrexate MTX is an analog of folic acid used for rheumatoid arthritis RA treatment since 1951 with anti-inflammatory, anti-proliferative and immunosuppressive

activity. Actually, MTX most important indications is the administration of RA and psoriatic arthritis PsA [4]. A low-dose from MTX (5–25 mg/week) utilized as treatment for autoimmune diseases, like PsA or RA and for can cer high-dose ( $\geq 500$  mg/m<sup>2</sup>) [5]. Many researches carried out in patients, in vitro and animals, to discuss the multiple courses which it may result in MTX hepatotoxicity. It find that aggregation and retention of MTX polyglutamates MTXPGs and folic acid depletion in cells of liver leads to high liver enzymes levels, which probably partially responsible for MTX hepatotoxicity [6]. A program of genetic cell death know as Apoptosis its functions to clear altered cells or senescent that are felled or useless in the organism that consistes of multiple cells. [7]. The damage DNA that cannot be repaired must sensed carefully so as to clear damaging cells. Cells of cancer develop mechanisms to evade apoptosis and competent to avoid signals of inhibition of growth [8]. The apoptosis machinery has main regulatory agents and effector agents. These arrangers are part of two main tours: first tour received and processed extracellular signs leading to death (extrinsic apoptotic program), The second tour detected and integrated intracellular signals (intrinsic apoptotic program). Both cercuits ending with generating the activation of a cascade of proteases synthesized as proenzymes, termed caspases which activated by proteolytic cleavage, which may cleave other caspases as part of signaling cascade of apoptosis [9, 10]. The activation of initiator caspases Casp 2, 8, 9 and 10, by pro-apoptotic signals, splite and activate effector caspases 3, 6 and 7 that activate apoptosis [11, 12]. Casp 3 is in charge of nuclear modifications, and its regard as the caspase which it is the main effector in extrinsic and intrinsic courses lead to activation of Casp 3 [13]. Researches showed that higher intakes of Cruciferous vegetables include broccoli, Brussels sprouts,

cabbage, cauliflower, turnips, wasabi etc reduce cardiometabolic diseases risk [14], musculoskeletal conditions [15], and tumors [16]. Broccoli sprouts (BS) contain various antioxidants like glucoraphanin GR, carotenoids, vitamins, and compounds of sulfur. One of this compounds, derive from GR called a sulforaphane SFN, which activate Kelch-like ECH-associated protein 1-nuclear factor (erythroid-derived 2)-like 2 (Keap1-Nrf2) pathway, and have anti-inflammatory and antioxidant activity [17]. Sulforaphane enhances productivity of glutathione and activates glutathione reductase, glutathione S-transferase, and glutathione peroxidase, to increase the rate of intracellular reduction [18]. SFN is a compound containing sulfur, water insoluble, but its precursor and form of storage in plants know as GR, soluble in water and its used in clinical research more than its pure form or in the form of sprout extracts and seed of broccoli . As an average, the pure SFN bioavailability is higher about seven fold more than GR [19]. The present research aimed to set the levels of caspase-3 and liver function to set the protective effects of BSE in mitigating the impact of MTX in rat female due to lack of studies that addressed this matter especially in females which spread among them lots of autoimmune diseases requires MTX use.

### **Materials**

30 female albino rat, average body weight 180-225 gm were obtained from animal house of the faculty of veterinary medicine in Tikrit university, Iraq used in this research. Rats were housed in metal cages with optimum environmental and nutritional conditions during period of experiment and seven days prior. The animals were divided into 6 groups every group consist of 5 animals, all of them administrated orally. Group(A) was negative control administrated with water only, group(B) received 0.15 mg/kg MTX weekly.

group (C) received BSE 5mg/kg daily, group (D) received BSE(7.5 mg group (E) received 0.15 mg MTX weekly and 5 mg/kg BSE daily and the last group (F) received 0.15 mg/kg MTX weekly and 7.5 mg/kg BSE daily.

**Dose preparation**

Methotrexate tablets 2.5 mg/kg were obtained from Medwise (UK) and crushed into powder and suspended in water. Dose of BSE selected based on [20] and doubled to ensure the effectiveness of the dose. Route of Administration selected based on [21]. MTX dose for rheumatoid arthritis, route of administration, and dosage calculation based on [22].

**Broccoli sprout extract powder preparation.**

Seeds of broccoli (*Brassica oleracea* Botrytis v. *Cymosa*) were obtained from Sgaravatti,

Italy. Seeds sprouted for five days to get sprouts and washed to purify them of seed husks and ungerminated seed [23]. BSE was prepared as mentioned in [24].

**Biological assays**

liver functions test in rat (GOT, GPT, ALP) were determined with kit (Agappe Pharmaceutical Co., Ltd, India), and Casp 3 gene expression was measured by using Bio-Rad CFX96 Touch Real-Time PCR System the start was RNA extraction by using Trans Zol Up Plus RNA kit, the other step transformation of ssDNA to cDNA as a first step according to the two-step thermal cycling method, after additions completing, samples were moved to a thermocycler so as to start the reaction. The initial denaturation step of program of thermal cycling 10 min at 25°, followed by annealing step 20 min at 42° C the last one, 5 s at 85° for extension. All kits that used was from TRANS

Table ( 1 ) Caspase-3 and Glyceraldehyde-3-phosphate dehydrogenase GADPH primer sequences for Real-Time PCR

primers	sequences
Caspase 3 Forward	GGTCATGGTTCATCCAGTC 20
Reverse Caspase 3	GGGATCTGTTTCTTTGCAT 20
ADPH Forward	ATCACTGCCACCCAGAAGACTG 23
ADPH Reverse	TGCCAGTGAGCTTCCCGTTCAG 23

The preparation of the qRT-PCR mixture was carried out carefully and meticulously. The additives of reaction mixture as mentioned in table ( 2), after complete the mixture, samples were moved to the device , following a specific program the intraction was started, the primary denaturation at 94°C for 5 s and

the second at 94°C for 5 s, by 45 cycles of a followed by step of annealing at 60°C for 10 s, the extension at 72°C for 10 s and the end was extension done for 5 min at 72°C.

Table ( 2 ) qRT-PCR reaction mixture

Primers	Quantities
μL	template cDNA
pmol, 0.5 μL	primer of forward
pmol, 0.5 μL	primer of reverse
μL	Perfectstart Green qPCR SuperMix
μL	Nase-free wat

**Statistical analysis**

Liver functions data presented as mean ± standard deviation (SD). SPSS 31.0 used to determine statistical analysis, largest arithmetic mean represented by (a) , symbol (c) the smallest and (bc) indicates that no significant difference.

**Result and discussion**

In this research levels of liver functions and caspase-3 have been identified to determine protective effects of BSE in reduce negative impact of MTX in rat female

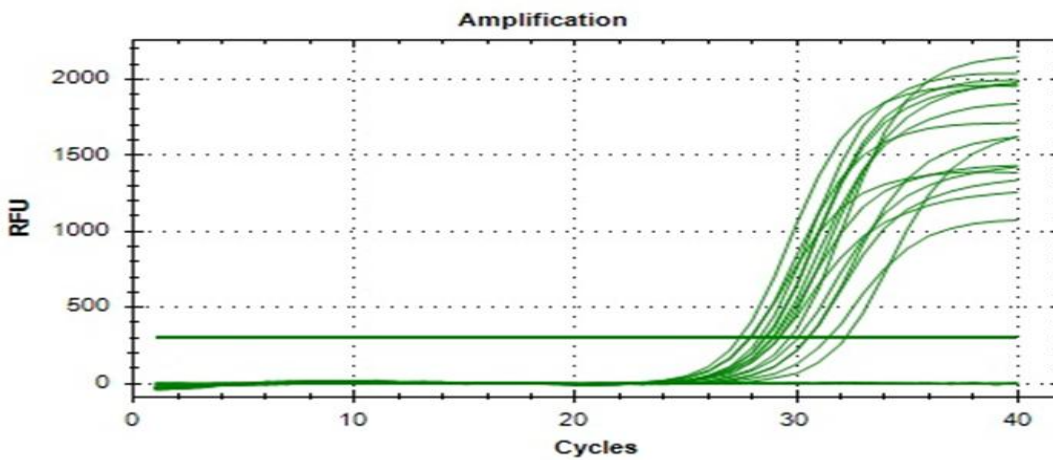


Figure (1) Amplification curve of casp3

**Table 3 explains the gene expression of caspase 3**

Group	Mean ± SD
Control -	1.05
MTX 0.15mg/ kg	1.50974906
BSE 5 mg / kg	1.5750102
BSE 7.5 mg / kg	1.5583481
MTX0.15mg/kg + BSE 5mg/ kg	1.5906878
MTX0.15mg/ kg + BSE 7.5mg/ kg	1.4541324

This table explain values of casp3 gene expression as we note the expression elevated in MTX group if we compared with control(1.05),this indicates an increase in apoptosis, these result consistant with [25] that mentioned treatment with MTX significantly increased activity ofcaspase-3 and Bax expression while levels of Bcl-2 expression decreased, and so creating an environment for apoptosis. we note too casp 3 expression was normal in groups those treated with BSE alone, and ingroups those treated with MTX and BSE, this indicates that it is safe and its improve the negative effects of MTX in case of its use to treat autoimmune diseases and cancers. [26] mentioned that SFNsafe for normal cells and have anticancer and cytotoxicity activity to alterd cells, after exposure to 20 µMfor 48 h of SFN, viability of about 70% of HepG2 cells inhibited but no high cytotoxicity observed in human hepatocytes cultured for 48 h and treated with 50 µM of SFN. The action mechanism of of SFN in BS, was inhibition of inflammatory cascade by reduce of MAPK signaling. SFN-enriched BS

reduced activation of the NF-κB signaling pathway by inhibit induce LPS- and inflammatory proteins secretions such as (COX-2,iNOS, IL-6 , TNF-α, , PGE2, IL-1β, etc.), which are responsible for the inflammatory cascades in both acute and chronic inflammation. It also upregulated the expression of Nrf2 and HO-1 in normal and activated microglia followed by the lowered neuronal apoptosis induced by activated microglia. Interestingly, BS enriched with SFN enhanced the scopolamine-induced memory impairment in mice by activate Nrf2, inhibiting apoptosis neuron by inhibit activation of of caspase-3 which caused neuroprotection against neurodegenerative disorder [27].

Table (4) showed variation between groups and negative control in(ALT), no significant differences if we compare control with 5 and 7.5 mg/ kg BSE , we can show significant difference between negative control (38.04 ± 2.53) and MTX 0.15mg/ kg but, the elevation of ALTwas not too high if we compare with control

**Table (4): Mean differences of ALT(GPT) values in (6) groups**

Group	Mean ± SE
Negative Control	38.04 ± 2.53 bc
MTX 0.15mg/ kg	66.53 ± 6.30 a
BSE 5 mg / kg	25.77 ± 1.58 c
BSE 7.5 mg / kg	27.70 ± 4.51 c
MTX 0.15 mg/kg + BSE 5mg/ kg	48.90 ± 2.85 b
MTX 0.15mg/kg + BSE 7.5mg/kg	35.48 ± 1.63 bc

**Figure(2) Mean differences of ALT(GPT)**

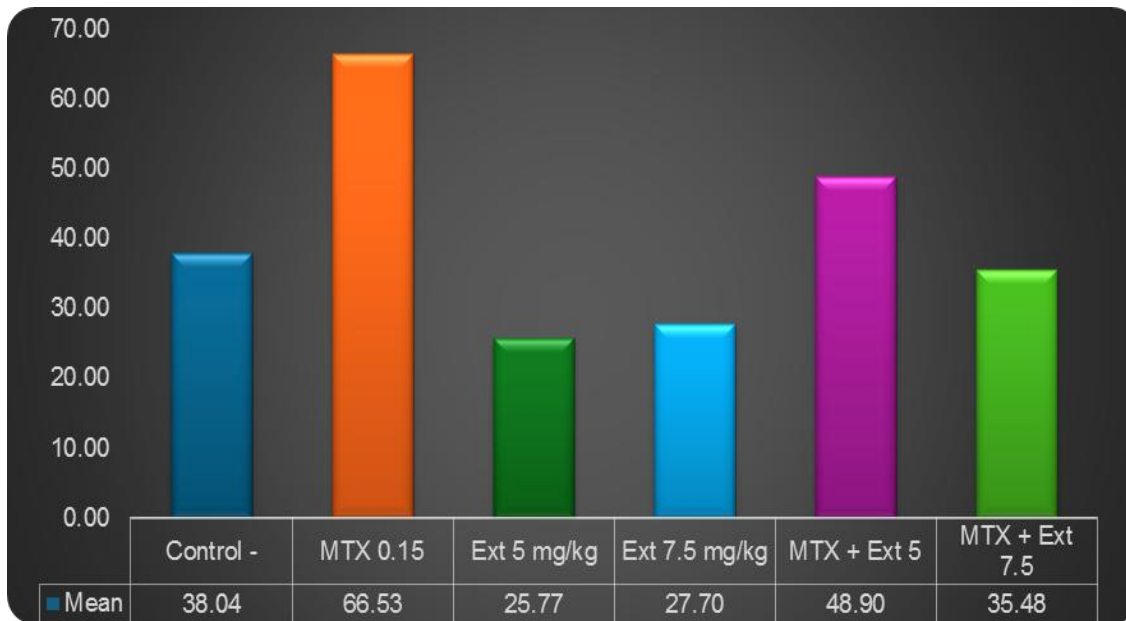


Table (5) explain differences in AST(GOT) between negative control (38.97 ± 2.36 ) As we note the elevation of AST was not very high if we compare with control. table show that BSE decrease level of (ALT)in5mg/ kg

and 7.5 mg/ kg BSE groups and in MTX 0.15mg/kg + BSE 5mg/ kg andMTX0.15mg/ kg + BSE 7.5mg/ kg5 if its compared with MTX 0.15mg/ kg that’s confirms the positive impact of BSE on liver

Table (5) explain differences in Mean of AST(GOT) in (6) groups in rat female

Group	Mean ± SE
Control -	39.97 ± 2.36 b
MTX 0.15mg/ kg	61.51 ± 5.12 a
BSE 5 mg / kg	30.63 ± 1.58 b
BSE 7.5 mg / kg	28.60 ± 5.26 b
MTX0.15mg/kg + BSE 5mg/ kg	34.59 ± 3.76 b
MTX0.15mg/ kg + BSE 7.5mg/ kg	36.00 ± 3.02 b

Figure (3) Mean of GOT

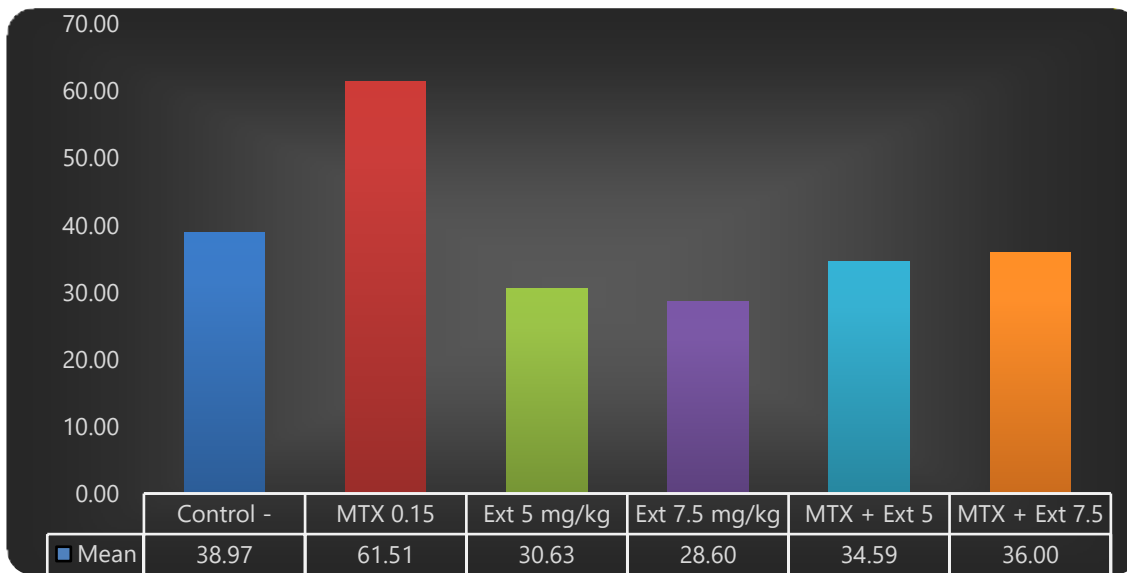


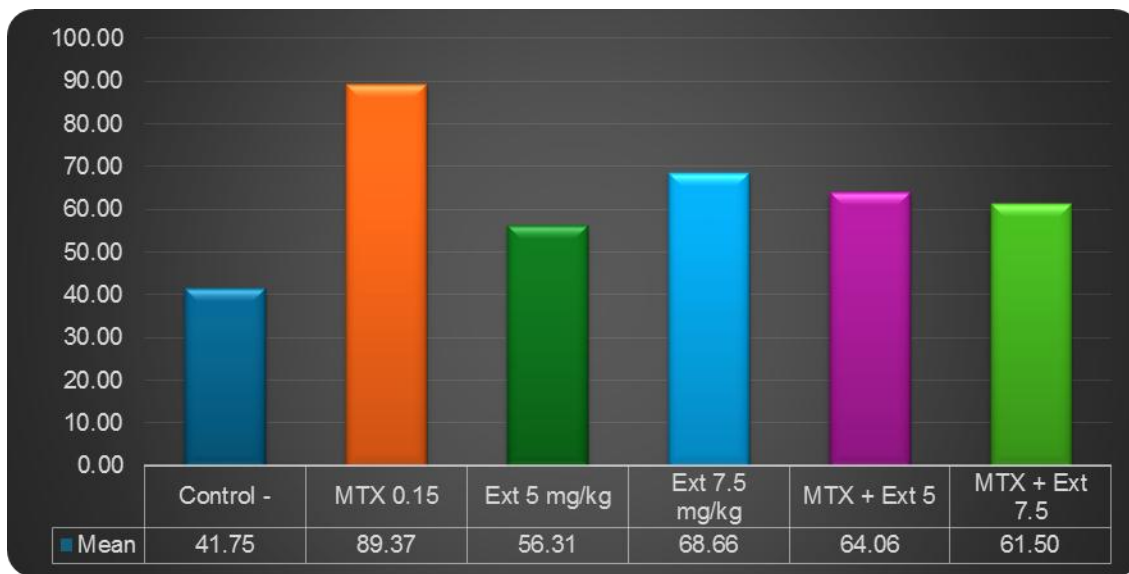
Table (6) explain differences in ALP between negative control(41.75 ± 5.45 ) table show that BSE decrease level of (ALP)in5mg/ kg and 7.5 mg/ kg BSE groups and in MTX0.15mg/kg + BSE 5mg/ kg

andMTX0.15mg/ kg + BSE 7.5mg/ kg5 if its compared with MTX 0.15mg/ kg (89.37 ± 4.53) In proportions close to negative control mean value.

Table (6) explain differences in Mean of ALP in (6) groups in rat female

Group	Mean ± SE
Control	41.75 ± 5.45 c
MTX 0.15mg/ kg	89.37 ± 4.53 a
Ext 5 mg / kg	56.31 ± 1.19 bc
Ext 7.5 mg / kg	68.66 ± 2.94 b
MTX0.15 mg/ kg + Ext 5 mg/ kg	64.06 ± 3.95 b
MTX 0.15mg/ kg + Ext 7.5mg/kg	61.50 ± 3.03 b

Figure (4) ALP Mean value



In the initial evaluation as in follow-up, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) determinations as markers of MTX toxicity were measured. To our knowledge, this is the only study to have carried out to estimate the impact of BSE to mitigate the negative effects of MTX on the liver functions and casp3 expression. Detected elevations of ALT/AST in hepatotoxicity in clinical practice and in some studies have no relation to MTX [4]. ALP were lowered significantly in groups treated with MTX and BSE groups if we compare with MTX group. There is not studies date describing BS preparations benefits or SF on the enhancement of liver disorders in humans, but there are many studies on animal have been demonstrated to describe SFN hepatoprotective effects [28]. Traditional studies in toxicology have explain that ingestion of GR or SFN which exists in BSE can prevent hepatotoxicity noticeably caused by a very wide range of chemicals that cause hepatotoxicity such as cisplatin, mycocyst in [28, 29]. These results consistent with [18] which were suggested that ingest of BS continuous for 2 mo affected participants physiologies and reduce oxidative stress beyond the placebo effect, that leads to liver function enhancement.

### **Conclusion**

Our study suggested that BSE enhance liver functions and caspase 3 expression in rat that treated with MTX and broccoli sprout extract and in groups treated with BSE only if we compared it with control and MTX groups.

### **Conflict of interest**

The authors declare that they have no conflict of interest.

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## التأثيرات الوقائية لمستخلص براعم البروكلي على الكاسبيز 3 ووظائف الكبد لدى إناث الجرذان المعالجة بالميثوتريكسات

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### الخلاصة

يعد الميثوتريكسيت نظيراً لحمض الفوليك يستخدم بجرعات منخفضة لعلاج أمراض المناعة الذاتية مثل التهاب المفاصل الصدفي أو الروماتيدي وجرعات عالية لعلاج السرطان. ويزيد من الموت المبرمج طريق تنشيط كاسبيز 3 الذي ينشط انزيم البروتياز المسبب للموت الخلوي. مما يحفز التجزئة المتخصصة لبروتينات الخلية. تم اختبار مستخلص براعم البروكلي في هذه الدراسة لأنه يحتوي على نسبة عالية من الكلوكورافانين مقارنة بالبروكلي الناضج. تهدف هذه الدراسة الى قياس مستويات كاسبيز 3 ووظائف الكبد لتحديد الآثار الوقائية لمستخلص براعم البروكلي في التخفيف من تأثير الميثوتريكسيت في إناث الجرذان بسبب قلة الدراسات التي تناولت هذا الموضوع خصوصاً في الإناث اللاتي تنتشر بينهن أمراض المناعة الذاتية التي تتطلب استخدام الميثوتريكسيت. تم استخدام تقنية تفاعل البوليميراز المتسلسل الكمي للتحليل وتحديد مستويات التعبير الجيني لكاسبيز 3 تقترح هذه الدراسة أن مستخلص براعم البروكلي يحسن وظائف الكبد والتعبير الجيني لكاسبيز 3 في الجرذان التي عوملت مع الميثوتريكسيت ومستخلص براعم البروكلي سوية أو في المجموعات التي عوملت مع المستخلص لوحده عند مقارنتها بمجموعتي السيطرة السالبة والموجبة التي عوملت مع الميثوتريكسيت لوحده

### الكلمات المفتاحية

ميثوتريكسيت، مستخلص براعم البروكلي , كاسباس 3، وظائف الكبد