

Efficacy and Safety of “URSA Complex” in Subjects with Physical Fatigue: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

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Abstract

Background: Fatigue is a common symptom both in diseases status and in healthy subjects. Various supplements and nutraceuticals for relieving of fatigue have been used. However, there are a few studies to evaluate the efficacy and the safety of the drug for fatigue alleviation, we conducted using URSA Complex to evaluate the efficacy on physical fatigue via score changes in the checklist individual strength (CIS).

Methods: The study was designed as a multicenter, randomized, double-blind, placebo-controlled trial, with subjects randomized to one of the two arms, receiving either placebo or URSA Complex administered as identical capsules. The primary efficacy endpoints of this clinical trials are the ratio of improving CIS scores < 76 points in patients at the end (4 weeks). Secondary efficacy variables are as follows one is an improvement of fatigue and the other is an improvement of the liver enzyme.

Results: The fatigue recovery rate in who had improved CIS scores of < 76 points were 70.0%, 50.9% in the therapy group and placebo group, respectively ($P = 0.019$). The fatigue recovery rate in CIS score was higher in URSA Complex therapy group than placebo group. The difference between therapy group and placebo group was statistically significant at 4 weeks later, but not 2 weeks.

Conclusions: Our results provided that the URSA Complex was effective in alleviating physical fatigue. The adverse event frequency in the therapy groups was similar to that in the placebo group.

Key words: Checklist Individual Strength; Efficacy; Physical Fatigue; Safety; URSA Complex

INTRODUCTION

Fatigue is a common symptom both in diseases status and in health. Fatigue can be defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion.^[1] Physical fatigue is the bodily experience of exhaustion following strenuous physical effort and mental or central fatigue is the subjective self-reported feeling of fatigue.^[2,3] We focused on physical fatigue and did not consider mental fatigue. Several studies have demonstrated that energy metabolism is involved in the pathophysiology of fatigue. Various supplements and nutraceuticals for relieving fatigue have been used. However, there are a few studies to evaluate the efficacy and the safety of the drug for fatigue alleviation.

URSA Complex have composite of ursodesoxycholic acid (UDCA) 25 mg, taurine 300 mg, dried ginseng extract 50 mg, inositol 10 mg, thiamine nitrate 5 mg. URSA Complex is used in alleviating physical fatigue and increasing stamina. UDCA is used in the treatment of cholestatic liver diseases,

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Received: 19-08-2015 **Edited by:** Yi Cui

How to cite this article: Kim KM, Kim MJ, Song SW, Cho DY, Park KC, Yang SW, Kim YS, Kim KS. Efficacy and Safety of "URSA Complex" in Subjects with Physical Fatigue: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial. Chin Med J 2016;129:129-34.

Access this article online

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DOI:
10.4103/0366-6999.173432

gallstone dissolution, fatty liver, and for patients with hepatitis virus infection to ameliorate elevated alanine aminotransferase (ALT) levels in East Asia.^[4-7] UDCA also has beneficial effects on liver regeneration with the nonalcoholic fatty liver disease.^[8] Suggested mechanisms of UDCA include the improvement of bile acid transport and/or detoxification, cytoprotection, and anti-apoptotic effects.^[9-12] UDCA activates AMP-activated protein kinase (AMPK) in the liver, suggesting that UDCA may act as an AMPK agonist.^[13] AMPK is known to play a major role in energy homeostasis. The other components of URSA Complex are taurine, dried ginseng extract, inositol, and thiamine nitrate were considered to have anti-fatigue effects.

Therefore, these observations suggest that URSA Complex has a beneficial effect on the regulation of energy production. However, there are no clinical trials on the effects of URSA Complex on physical fatigue. In this study, a multicenter, randomized, double-blind, placebo-controlled trial was conducted using URSA Complex, which has been approved as having the effects of fatigue recovery and ergogenic aid, to evaluate the efficacy of URSA Complex on physical fatigue via score changes in the checklist individual strength (CIS).

METHODS

Study design

Study patients were recruited from an individual who visited 1 of 4 medical centers in Korea from October 2014 to March 2015, those who had persistent fatigue for ≥ 1 month were selected. Patients who met the following criteria were eligible for this study: (1) >19 years old, (2) persistent or chronic fatigue for ≥ 1 month on screening, (3) total CIS score ≥ 76 points on screening and baseline, (4) Hospital Anxiety and Depression Scale (HADS) ≤ 10 points on screening, and (5) voluntarily agreed on consent information to fully understand and participate in clinical trials.

Patients were excluded from the study if they met one of the following conditions: (1) diseases/conditions that cause fatigue such as chronic viral hepatitis B or C, viral hepatitis B carrier, hepatic dysfunction (2 times more than the normal upper limit in any of the followings: serum aspartate aminotransferase [AST], ALT, alkaline phosphatase, and total bilirubin), liver cirrhosis, alcoholic/nonalcoholic steatohepatitis, renal dysfunction (2 times more than the normal upper limit in serum creatinine), chronic fatigue syndrome, (2) the following underlying diseases were identified (malignant tumor, active pulmonary tuberculosis, asthma, glaucoma, multiple sclerosis, hypothyroidism, chronic inflammatory diseases such as rheumatoid arthritis, etc.), (3) psychiatric diseases (major depressive disorder, bipolar disorder, schizophrenia, delusional disorder, dementia, etc.), (4) uncontrolled hypertension ($\geq 170/110$ mmHg), uncontrolled diabetes (HbA1c $\geq 8.0\%$), and obesity (body mass index ≥ 30), (5) taking medicine that cause fatigue such as beta-blockers, glucocorticoids, immune modulators, and antidepressants.

The protocol was approved by the ethics committee of each institution participating in the study. Patients were informed of the details of the clinical study and agreed to participate. We conducted this clinical study in accordance with the Declaration of Helsinki and good clinical practice. This study was registered with ClinicalTrials.gov (NCT 02418130).

Sample size determinations

The primary objective of this trial was to evaluate the rate of improvement in fatigue symptoms CIS scores during the study by drug administration to determine the statistical superiority compared to placebo. The assumed ratio of CIS scores improved to < 76 points is 71% in the therapy group for 4 weeks, otherwise assumed to be 44% in the placebo group. When this study would be tested under the circumstances of the two-sided significance level of 0.05, a statistical power of 90%, 1:1 assignment, the minimum required a number of this test subjects was calculated as 66 people per group. The minimum required number of test subjects was calculated as 66 people per group taking into account the 20% drop out, we registered participants of 83 people per group (166 patients).

Fatigue assessment

Efficacy was evaluated at the baseline visit and after each treatment phase using the following self-administered measures of fatigue: CIS (the questionnaire had 20 items, and a maximum of 7 points was given to each item. Higher total scores reflected a higher degree of fatigue. In this study, the criterion of the CIS score for the subject selection was 76 points). The CIS covers several aspects of fatigue, such as severity, motivation, concentration, and physical activity level, which fit in with the concept of prolonged fatigue. The CIS total cut-off of >76 was based on high specificity, considering a minimum of false-positively classified healthy working employees.^[14] The defined CIS total cut-off point should be regarded as a score indicating a fatigue level that puts the individual "at risk" for sick leave or work disability, and seemed to be appropriate for use in fatigue studies in the working population.^[15]

Study design

The study was designed as a multicenter, randomized, double-blind, placebo-controlled trial, with subjects randomized to one of the two arms, receiving either placebo or URSA Complex administered as identical capsules. After providing informed consent, their medical history and records, laboratory test results, and CIS and HADS were reviewed. The subjects were randomized to treatment or placebo and took either placebo or URSA Complex twice daily for 4 weeks. During the study, additional exclusion criteria such as anemia and nutritional deficiency were applied [Figure 1]. Treatment or evaluation was discontinued because of patient request, adverse events, or other reasons. CIS, vital sign including blood pressure, pulse pressure, and laboratory examinations were assessed at baseline, 2 weeks, 4 weeks after from the starting time of this study. Adverse events, together with their severity and perceived relation to study medication, were recorded throughout the study. Serious adverse events (e.g., those requiring admission to

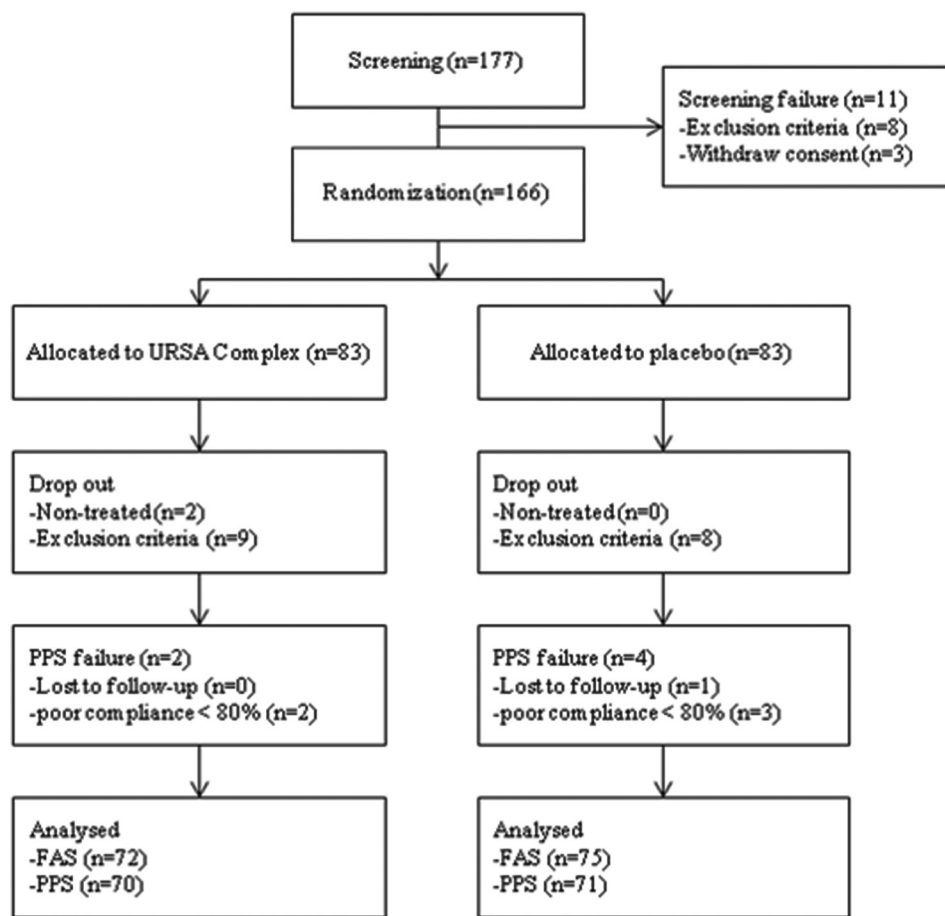


Figure 1: Study participation flow chart. FAS: Full analysis set; PPS: Per-protocol set.

hospital or that resulted in a persistent or significant disability or incapacity) were also recorded.

The primary efficacy endpoints of this clinical trials were ratio of improving CIS scores < 76 points in patients at the end (4 weeks). Secondary efficacy variables were an improvement of fatigue and improvement of the liver enzyme.

Statistical analysis

SAS™ System (SAS Institute, Inc., Cary, NC, USA) version 9.3 was used for the statistical analysis. The Pearson's Chi-square test or Fisher's exact test was conducted to investigate the difference in the frequency and proportion of the subjects who had improved CIS scores of < 76 points which was found among the subject groups, to compare the categorical variables of secondary efficacy endpoint between groups, and to compare the difference of adverse events prevalence between groups. In addition, the two sample *t*-test or Wilcoxon rank sum test was conducted to investigate the difference of continuous variables between groups depending on normal distribution.

A paired *t*-test or Wilcoxon signed rank test was conducted to compare the difference of laboratory test and vital signs between the group and McNemar's test was conducted to compare the difference of categorical variables between group.

RESULTS

General characteristics

Baseline characteristics of the subjects. No significant differences in all characteristics except sex were found between groups. There were more male participants in URSA Complex than placebo, but no significant difference in CIS scores was existed between men and women (data not shown). Therefore, it was presumed that sex difference would not affect the comparison of groups when the primary efficacy endpoint was assessed with the CIS recovery amount or rate. The mean values of CIS scores were 91.5, 93.4 in the test group and placebo group, respectively [Table 1].

Fatigue recovery rate of the checklist individual strength score

In full analysis set, the fatigue recovery rate in subjects with improved CIS scores of < 76 points were 69.4%, 52.0% in therapy group and placebo group, respectively ($P = 0.031$). Moreover, per-protocol analysis set, those in who had improved CIS scores of < 76 points were 70.0%, 50.7% in the therapy group and placebo group, respectively ($P = 0.019$). The fatigue recovery rate in CIS score was higher in URSA Complex therapy group than placebo group. The difference between therapy group

and placebo group was not found statistically at 2 weeks later, but after 4 weeks, the difference between groups was significant [Figure 2].

Changes of checklist individual strength scores during the study

No statistically significant change of fatigue scores were found between therapy group and placebo group during 4 weeks study period, but fatigue scores in CIS were decreased in the therapy group and placebo group from 2 weeks later to 4 weeks later. Mean change of CIS scores during 4 weeks study period were 21.9 score decrease, 22.2 score decrease in the therapy group and placebo group, respectively [Table 2]. Mean CIS score of therapy group at endpoints (4 weeks) was below 70, it was sufficiently decreased below of CIS scores 76 points, meaningful point as fatigue cut-off value.

Changes of blood chemistry during the study

No difference of change in AST or gamma glutamyl transpeptidase during the study was observed between therapy group and placebo group at 4 weeks ($P = 0.927$ or $P = 0.814$ respectively), but the difference of change in ALT was significant ($P = 0.013$) between therapy group and placebo group. The mean decreases in serum ALT levels from the baseline value to 2 weeks later or 4 weeks later were 4.1, 2.8 IU/L in therapy group, respectively. The mean decreases in serum AST levels from the baseline value to 2 weeks later or 4 weeks later were 5.7, 4.0 IU/L in therapy group, respectively. The difference of change in AST between therapy group and placebo group was statistically significant at 2 weeks later, but not after 4 weeks [Table 3].

Safety assessment

The percentages of the subjects who experienced adverse events was not significantly different between URSA Complex group and placebo group ($P = 0.068$) [Table 4]. Adverse events in URSA Complex group were nasopharyngitis, gastroenteritis, herpes zoster, hand fracture,

contusion, constipation, nausea, blepharospasm, dizziness, back pain, and wisdom tooth extraction, respectively. In the placebo group, adverse events were periodontitis, upper respiratory infection (8 persons), constipation, aphthous stomatitis, gastritis, the sensitivity of teeth, muscle strain, glaucoma, headache, contact dermatitis, and skin rash, respectively. In this clinical trial, 1 subject in placebo experienced adverse drug reaction such as rash, but its causal relationship between placebo drug and skin rash was not clear. Serious adverse events did not occur in both groups.

Table 1: Baseline characteristics of the subjects

Index	URSA complex (n = 72)	Placebo (n = 75)	P
Gender, n (%)			
Men	23 (31.9)	15 (17.3)	0.040
Women	49 (68.1)	62 (82.7)	
Age (years), n (%)			
<29	27 (37.5)	23 (30.7)	0.717
30–39	25 (34.7)	36 (48.0)	
40–49	16 (22.2)	13 (17.3)	
>50	4 (5.6)	3 (4.0)	
BMI (kg/m ²), mean ± SD	21.9 ± 2.7	21.9 ± 2.6	0.956
Smoking, n (%)			
Non	63 (87.5)	65 (86.7)	0.571
Past	4 (5.6)	7 (9.3)	
Present	5 (7.0)	3 (4.0)	
Alcohol drinking, n (%)			
Non	32 (44.4)	37 (49.3)	0.553
Past	0 (0.0)	0 (0.0)	
Present	40 (55.6)	38 (50.7)	
Caffeine drinking, n (%)			
No	19 (26.4)	13 (17.3)	0.184
Yes	53 (73.6)	62 (82.7)	
HADS, mean ± SD			
Anxiety	5.0 ± 2.6	5.0 ± 2.6	0.936
Depression	6.4 ± 2.7	5.8 ± 2.7	0.356
ALT (U/L)	17.6 ± 9.5	16.7 ± 11.5	0.699
AST (U/L)	22.7 ± 26.6	20.1 ± 10.5	0.433
γ-GT (U/L)	18.3 ± 14.0	18.4 ± 18.8	0.972
Albumin (g/dl)	4.6 ± 0.3	4.6 ± 0.3	0.191
T-bilirubin (mg/dl)	0.6 ± 0.3	0.6 ± 0.3	0.720
CIS score	91.5 ± 10.6	93.4 ± 11.5	0.293

Data are shown as n (%) or mean ± SD. BMI: Body mass index; HADS: Hospital Anxiety and Depression Scale; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γ-GT: Gamma glutamyltranspeptidase; T-bilirubin: Total bilirubin; CIS: Checklist individual strength; SD: Standard deviation.

Table 2: Changes of CIS during the study

Groups	CIS score			P
	Baseline	2 weeks change	4 weeks change	
URSA complex	91.5 ± 10.6	-11.7 ± 10.9	-21.9 ± 15.2	0.856
Placebo	93.4 ± 11.5	-13.8 ± 13.9	-22.2 ± 18.2	

Values are presented as mean ± SD. CIS: Checklist individual strength; SD: Standard deviation.

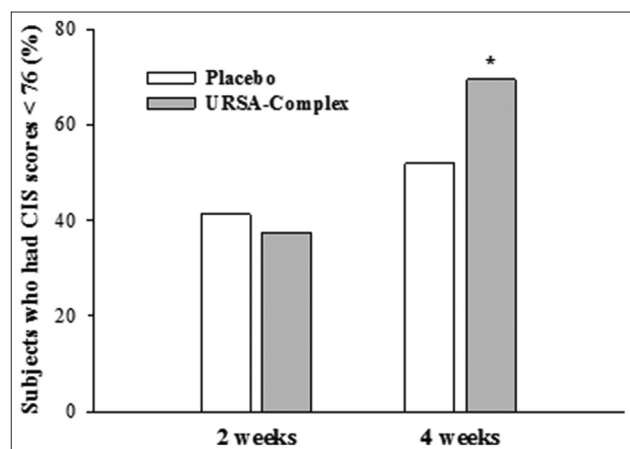


Figure 2: Proportion of the subjects who had improved CIS scores of <76 points between the subject groups at 2 weeks and 4 weeks. CIS: Checklist individual strength (* $P < 0.05$).

Table 3: Changes of blood chemistry including liver enzymes during the study

Index	Baseline	2 weeks change	4 weeks change	P
ALT (U/L)				
URSA complex	17.6 ± 1.1	-4.1 ± 0.8	-2.8 ± 0.9	0.013
Placebo	16.9 ± 1.3	-0.4 ± 1.2	-0.9 ± 1.1	
AST (U/L)				
URSA complex	22.7 ± 3.1	-5.7 ± 3.1	-4.0 ± 3.2	0.927
Placebo	20.1 ± 1.2	-0.4 ± 1.2	-1.9 ± 1.1	
γ-GT (U/L)				
URSA complex	18.3 ± 1.6	-0.9 ± 0.5	-1.3 ± 0.8	0.814
Placebo	18.4 ± 2.2	-0.6 ± 0.6	-1.1 ± 0.6	

Values are presented as mean ± SE. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γ-GT: Gamma glutamyltranspeptidase; SE: Standard error.

Table 4: Comparison of adverse events among groups

Index	URSA complex (n = 81)	Placebo (n = 83)	P
Adverse events	9 (11)	18 (22)	0.068
Adverse drug reactions	0 (0)	1 (1)	1.000
Serious adverse events	0 (0)	0 (0)	–

Values are presented as n (%).

DISCUSSION

This study, which to our knowledge, represents the first study to show that URSA Complex can induce recovery from physical fatigue subjects. It demonstrates that the fatigue recovery rate in subjects with improved CIS scores of < 76 points was higher in URSA Complex therapy group than placebo group. We observed that the mean decrease in serum ALT levels from the baseline value to 4 weeks endpoints later was higher in the therapy group than placebo group.

The fatigue recovery rate in CIS scores was above 50% in placebo, this study showed a relatively higher placebo effect than other studies.^[16,17] There cognition that URSA Complex would be effective to detoxify liver was widely distributed through advertizing for several decades. Therefore, Koreans had a high expectation that this drug would be effective to relieve fatigue. The placebo used in this study had a similar taste and smell and shape, so the high placebo effects might be due to the high expectation that received drug would be URSA Complex. The second reason to show no difference in groups was the short duration of this study. The 4 weeks period might be insufficient to demonstrate the physical fatigue efficacy. In this study, the fatigue recovery rate in subjects with improved CIS scores of < 76 points were increased in therapy group during 4 weeks. However, the fatigue recovery rate in subjects with improved CIS scores of < 76 points were not increased significantly in the placebo group from 2 weeks to 4 weeks. The third reason was that fatigue originated from multiple causes, and fatigue was hard to assess objectively.^[2] Fatigue scores such as CIS are used in studying fatigue and do not present the whole aspects of fatigue.^[18]

The underlying mechanism of the anti-fatigue action of UDCA is not known, but 5'-AMPK activation may be involved. UDCA strongly increases AMPK phosphorylation,^[13] and AMPK is a key regulator of cellular and whole-body energy balance.^[19] AMPK phosphorylates and regulates many proteins involved in nutrient metabolism, largely acting to suppress anabolic ATP-consuming pathways while stimulating catabolic ATP-generating pathways.^[20] Therefore, these observations suggested that UDCA has a beneficial effect on the regulation of energy production. The other mechanism is UDCA decreases hepatocyte sensitivity to hydrophobic bile acid-induced oxidative stress.^[11,12] Several studies found a significant association between lipid oxidation levels and fatigue.^[21,22]

The other components of URSA Complex are taurine, dried ginseng extract, inositol and thiamine nitrate. Taurine administration maintains its concentration in skeletal muscle after exercise and upregulates physical endurance and hence, was considered to reduce the exercise-induced muscle fatigue.^[23] Anti-fatigue effect might be due to enhance mitochondrial function and the regulation of cytoplasmic and mitochondrial calcium homeostasis.^[24] Anti-fatigue effect of ginseng extract, might be due to through protection of corpuscular membrane by preventing lipid oxidation via modifying several enzyme activities.^[25,26] Another reason for the anti-fatigue effect of ginseng extract, could involve triglyceride (TG) mobilization during exercise. Such an effect might become advantageous during prolonged exercise since better utilization of TG allows the sparing of glycogen and glucose and, therefore, delays fatigue.^[25] Inositol is part of the membranes of all cells and plays a role in helping the liver process fats as well as contributing to the function of muscles and nerves.^[27] The phosphoinositol/inositol phosphate is considered to have a role in second messenger system in modulating the calcium signaling resulting muscle depolarization, and this system were suggested to adapt to increased chronic muscle activity and might play a role in anti-fatigue effect.^[27] Thiamine is a coenzyme of carbohydrate and amino acid metabolism and plays an important role in ATP biosynthesis. Decreasing the thiamine in the cell degrades enzyme activation, decreases ATP biosynthesis and causes fatigue. The thiamine supplementation brings significant effect on the energy metabolism during exercise, it also positively affects anti-fatigue.^[28]

In this study, URSA Complex would be free from serious adverse events, adverse drug reactions, the frequency of its adverse events was also low.

This study is valuable as a multicenter, double-blind study that first assessed the efficacy and safety of the URSA Complex on physical fatigue. URSA Complex would be one of the treatment options for physical fatigue patients who have only effective therapeutic modalities currently available. It is not recommended to extrapolate this result to diseased patients. Further studies are needed to investigate anti-fatigue efficacy for disease-related fatigue patients.

In conclusion, the URSA Complex was effective in alleviating physical fatigue. The adverse event frequency in the therapy groups was similar to that in the placebo group.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. *Curr Opin Neurol* 1996;9:456-60. doi: 10.1097/00019052-199612000-00011.
2. Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. *Rheumatology (Oxford)* 2011;50:1009-18. doi: 10.1093/rheumatology/keq454.
3. Berrios GE. Feelings of fatigue and psychopathology: A conceptual history. *Compr Psychiatry* 1990;31:140-51. doi: 10.1016/0010-440X(90)90018-N.
4. Saksena S, Tandon RK. Ursodeoxycholic acid in the treatment of liver diseases. *Postgrad Med J* 1997;73:75-80. doi: 10.1136/pgmj.73.856.75.
5. Copaci I, Micu L, Ilescu L, Voiculescu M. New therapeutical indications of ursodeoxycholic acid. *Rom J Gastroenterol* 2005;14:259-66.
6. Sato S, Miyake T, Tobita H, Oshima N, Ishine J, Hanaoka T, *et al.* A dose-up of ursodeoxycholic acid decreases transaminases in hepatitis C patients. *World J Gastroenterol* 2009;15:2782-6. doi: 10.3748/wjg.15.2782.
7. Omata M, Yoshida H, Toyota J, Tomita E, Nishiguchi S, Hayashi N, *et al.* A large-scale, multicentre, double-blind trial of ursodeoxycholic acid in patients with chronic hepatitis C. *Gut* 2007;56:1747-53. doi: 10.1136/gut.2007.120956.
8. Xiang Z, Chen YP, Ma KF, Ye YF, Zheng L, Yang YD, *et al.* The role of ursodeoxycholic acid in non-alcoholic steatohepatitis: A systematic review. *BMC Gastroenterol* 2013;13:140. doi: 10.1186/1471-230X-13-140.
9. Ikegami T, Matsuzaki Y. Ursodeoxycholic acid: Mechanism of action and novel clinical applications. *Hepatol Res* 2008;38:123-31. doi: 10.1111/j.1872-034X.2007.00297.x.
10. Woollett LA, Buckley DD, Yao L, Jones PJ, Granholm NA, Tolley EA, *et al.* Effect of ursodeoxycholic acid on cholesterol absorption and metabolism in humans. *J Lipid Res* 2003;44:935-42. doi: 10.1194/jlr.M200478-JLR200.
11. Buryova H, Chalupsky K, Zbodakova O, Kanchev I, Jirouskova M, Gregor M, *et al.* Liver protective effect of ursodeoxycholic acid includes regulation of ADAM17 activity. *BMC Gastroenterol* 2013;13:155. doi: 10.1186/1471-230X-13-155.
12. Amaral JD, Viana RJ, Ramalho RM, Steer CJ, Rodrigues CM. Bile acids: Regulation of apoptosis by ursodeoxycholic acid. *J Lipid Res* 2009;50:1721-34. doi: 10.1194/jlr.R900011-JLR200.
13. Nakagawasai O, Yamada K, Nemoto W, Fukahori M, Tadano T, Tan-No K. Liver hydrolysate assists in the recovery from physical fatigue in a mouse model. *J Pharmacol Sci* 2013;123:328-35. doi: 10.1254/jphs.13084FP.
14. Bültmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant I. Measurement of prolonged fatigue in the working population: Determination of a cutoff point for the checklist individual strength. *J Occup Health Psychol* 2000;5:411-6. doi: 10.1037/1076-8998.5.4.411.
15. Beurskens AJ, Bültmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: Validity of a questionnaire measure. *Occup Environ Med* 2000;57:353-7. doi: 10.1136/oem.57.5.353.
16. Lee KK, Choi WS, Yum KS, Song SW, Ock SM, Park SB, *et al.* Efficacy and safety of human placental extract solution on fatigue: A double-blind, randomized, placebo-controlled study. *Evid Based Complement Alternat Med* 2012;2012:130875. doi: 10.1155/2012/130875.
17. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: Randomised controlled trial. *BMJ* 2005;330:14. doi: 10.1136/bmj.38301.587106.63.
18. Shahid A, Shen J, Shapiro CM. Measurements of sleepiness and fatigue. *J Psychosom Res* 2010;69:81-9. doi: 10.1016/j.jpsychores.2010.04.001.
19. Grahame Hardie D. AMP-activated protein kinase: A key regulator of energy balance with many roles in human disease. *J Intern Med* 2014;276:543-59. doi: 10.1111/joim.12268.
20. Viollet B, Guigas B, Leclerc J, Hébrard S, Lantier L, Mounier R, *et al.* AMP-activated protein kinase in the regulation of hepatic energy metabolism: From physiology to therapeutic perspectives. *Acta Physiol (Oxf)* 2009;196:81-98. doi: 10.1111/j.1748-1716.2009.01970.x.
21. Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. *Free Radic Biol Med* 2005;39:584-9. doi: 10.1016/j.freeradbiomed.2005.04.020.
22. Maes M, Twisk FN. Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways. *BMC Med* 2010;8:35. doi: 10.1186/1741-7015-8-35.
23. Yatabe Y, Miyakawa S, Miyazaki T, Matsuzaki Y, Ochiai N. Effects of taurine administration in rat skeletal muscles on exercise. *J Orthop Sci* 2003;8:415-9. doi: 10.1007/s10776-002-0636-1.
24. Dawson R Jr, Biasetti M, Messina S, Dominy J. The cytoprotective role of taurine in exercise-induced muscle injury. *Amino Acids* 2002;22:309-24. doi: 10.1007/s007260200017.
25. Wang J, Li S, Fan Y, Chen Y, Liu D, Cheng H, *et al.* Anti-fatigue activity of the water-soluble polysaccharides isolated from *Panax ginseng* C. A. Meyer. *J Ethnopharmacol* 2010;130:421-3. doi: 10.1016/j.jep.2010.05.027.
26. Kim HG, Cho JH, Yoo SR, Lee JS, Han JM, Lee NH, *et al.* Antifatigue effects of *Panax ginseng* C.A. Meyer: A randomised, double-blind, placebo-controlled trial. *PLoS One* 2013;8:e61271. doi: 10.1371/journal.pone.0061271.
27. Oueslati H, Gardiner P. The effect of endurance training on phosphoinositide metabolism of extensor digitorum longus in rat. *Can J Appl Physiol* 2000;25:153-64. doi: 10.1139/h00-011.
28. Choi SK, Baek SH, Choi SW. The effects of endurance training and thiamine supplementation on anti-fatigue during exercise. *J Exerc Nutrition Biochem* 2013;17:189-98. doi: 10.5717/jenb.2013.17.4.189.