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The Effect of *Laetiporus* sp. (Bull. ex Fr.) Bond. et Sing. (Polyporaceae) Extract on Total Blood Cholesterol Level

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Abstract: A study on the effect of a local medicinal mushroom, *Laetiporus* sp. (Polyporaceae) extract on total blood cholesterol level has been conducted using Wistar rats with high cholesterol feed and prophylthiouracil (PTU) as hypercholesterolemia inducing agent. The study was aimed to evaluate the inhibition and reduction effect of the dried (hot water) extract of grain grown mycelia on hypercholesterolemia of the rat model. The rats were randomly classified into tested group and control group, each group consists of six rats. After a preliminary study, two doses level of the extract, i.e., 55 and 110 mg kg^{-1} b.wt. were tested, respectively. Commercial lovastatin tablet at a dose of 1.8 mg kg^{-1} b.wt. was also incorporated in the test as reference medicine. Total blood cholesterol level was observed once a week over 4 weeks. The trial was also conducted on human by involving 19 volunteers. They were asked to consume one *Laetiporus* sp. capsule per day after meal before going to bed over 30 days. The fungal extract at dose 55 mg kg^{-1} b.wt. could inhibit the blood cholesterol level by an average of 11.0% and dose 110 mg kg^{-1} b.wt. could inhibit by an average of 19.0% compared to commercial lovastatin at dose 1.8 mg kg^{-1} b.wt. which could inhibit at an average of 14.6% over 4 weeks. On the other hand, dose 110 mg kg^{-1} b.wt. could reduce blood cholesterol level by an average of 11.4%, compared to commercial lovastatin tablet which could reduce by an average of 5.5% over 4 weeks. In addition, blood cholesterol level was found to be reduced in 14 out of 19 (73.6%) of human volunteers while 5 out of 19 (26.4%) were increased. It is concluded that the mycelial extract of *Laetiporus* sp. is potential to be used as an anti hypercholesterolemia agent.

Key words: *Laetiporus* sp., Polyporaceae, medicinal mushroom, anti-hypercholesterolemia, lovastatin

INTRODUCTION

Laetiporus sp. is one species of brown rot fungi. It is a wild macro fungi (Basidiomycete) growing around tropical-subtropical area including Indonesia. There is very little study on local (Indonesian) medicinal mushroom including *Laetiporus* sp. has been done. Other species of *Laetiporus* such as *Laetiporus sulphureus* has been well known for their medicinal properties. For example, methanol and dichloromethane extracts of *Laetiporus sulphureus* was reported to exhibit high pancreatic lipase inhibitory activity (83±5%) (Slanc *et al*., 2004). A new lanostanoid triterpene, 3-oxosulfurenic acid (1), together with three known triterpenes (3, 4 and 7) were isolated from the fruit bodies of *Laetiporus sulphureus* which show cytotoxicity effect on human myeloid leukemia HL-60 cells (Leon *et al*., 2004).

Our previous findings demonstrated that local *Laetiporus* sp. isolated from West Java-Indonesia, contained lovastatin (Aryantha and Sidharta, 2007). Lovastatin which has been reported as an anti hypercholesterolemia substance was initially isolated from microfungi (*Penicillium citrinum*) (Endo *et al*., 1976). Recently, some edible mushrooms have been identified to posses anti hypercholesterolemia. *Inonotus obliquus* extract was found to be significantly reduced total cholesterol and triglyceride while increased high-density lipoprotein cholesterol level in serum of diabetic mice (Lu *et al*., 2010). Commercial button mushroom (*Agaricus bisporus*) was also reported to reduce plasma total cholesterol (TC) and low-density lipoprotein (LDL) of rat by 22.8 and 33.1%, respectively after 4 weeks of treatment (Jeong *et al*., 2010). Furthermore, Zhang *et al*. (2009) reported that *Tremella aurantialba* extracts has strong

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abilities to reduce the levels of total cholesterol and total triglyceride in serum of rats. In addition, *Hypsizygus marmoreus* (Bunashimeji), *Pleurotus eryngii* (Eringi) and *Grifola frondosa* (Maitake) were also reported to be significantly lower serum total cholesterol of mice at week 8, 10, 12, 14 and 16 after treatment (Mori *et al*., 2008).

The hypercholesterolemia is generally defined as a condition in which the concentration of cholesterol carrying lipoproteins in plasma exceeds an arbitrary normal limit. Clinical concern arises because an elevated concentration of blood lipid content (cholesterol and triglycerides) can accelerate the development of atherosclerosis, with its dual sequelae of thrombosis and infraction. The normal blood cholesterol level is less or equal to 200 mg dL^{-1}. The blood cholesterol level higher than 265 mg dL^{-1} increasing heart attack risk by 5 times (Gilman *et al*., 1990). This study was to find out the ability of the mycelial (hot water) extract of local *Laetiporus* sp. to inhibit and to reduce the hypercholesterolemia in Wistar female rats.

MATERIALS AND METHODS

This research was carried out during January 2008 to December 2008.

Anti-hypercholesterolemia material: Pure culture of *Laetiporus* sp. was sub cultured on Potato Dextrose Agar (PDA) plate and incubated over 5 days at room temperature. This agar culture was then cut into 1×1 cm^2 with scalpel aseptically before being inoculated into sterile cereal based medium consisting of broken corn (25%), red rice (15%), sawdust (50%), rice bran (10%) on dry weight based. After 1 month incubation at cereal based medium, the mycelial culture was ready to be extracted. The whole growing mycelia along the substrate were collected and extracted in boiling water for 30 min and then filtered. The water extract were then evaporated and dried. Brown dry extract with specific taste and odor was made into powder. Commercial lovastatin tablet was used as a reference medicine. The suspension of lovastatin was prepared in 1% solution of tragacanth with dose 1.8 mg kg^{-1} b.wt.

Hypercholesterolemia inducing agent consists of high cholesterol feed and prophylthiouracil (PTU). The high cholesterol feed was made of 15% of duck egg yolk, 10% of chicken liver, 15% of lamb fat and 60% of standard feed for rat. The solution of 0.1% PTU was also fed to the rat *ad libitum*.

Assay animal: Wistar female rats with 160-200 g of body weight prepared by Center for Life Science Institut Teknologi Bandung, Indonesia.

Toxicity analysis: Five animals both male and female were randomly chosen to do the toxicity test. Five doses of *Laetiporus* sp. extracts i.e., 1,250 (D1250); 2,500 (D2500); 5,000 (D5000); 7,500 (D7500) and 10,000 (D10000) (mg kg^{-1} b.wt.) were examined on assay animal and compared with control (no extract added). The animals were first observed for the growth pattern by weighing the body weight daily over 14 days. In addition, standard pharmacology activities including: visit up, visit down, motoric normal, motoric up, motoric down, straub, piloerection, ptosis, corneal reflex, pineal reflex, lacrimation, vasodilatation, catalpesy, hanging, retablishment, walking backward, walking forward, flexy, harfner respond, wriggling, grooming, tremor, body trembling, vocalization, urination and defecation of the animal were observed over 3 min per period of observation. After 14 days, the animals were killed for analyzing the internal organs including lung, heart, kidney, testis, spleen, liver and vesica seminalis. The organ index was calculated based on the ratio between the weight of the organ and the body.

Anti-cholesterol experimental method

There were two experimental methods: Cholesterol inhibition method and cholesterol reducing method. Preliminary study was done to find out reasonable doses of *Laetiporus* sp. extracts before determining the working doses both for inhibition and reducing methods.

Inhibition method, the animals were randomly classified into 4 groups: (1) control, (2) *Laetiporus* sp. mycelial extract at dose 55 mg kg^{-1} b.wt. (3) *Laetiporus* sp. mycelial extract at dose 110 mg kg^{-1} b.wt. (4) lovastatin at dose 1.8 mg kg^{-1} b.wt. Each group consists of 6 rats. The high cholesterol feed and PTU were administered simultaneously with the testing medicine orally once a day over 28 days.

Reducing method, the animals were randomly classified into 3 groups : (1) control (2) *Laetiporus* sp. extract at dose 110 mg kg^{-1} b.wt. (3) lovastatin at dose 1.8 mg kg^{-1} b.wt. Each group consists of 6 rats. The high cholesterol feed and PTU were given over 4 weeks (28 days) to make hypercholesterolemia. At day 29, the blood samples were collected from the tail vein to determine the starting high cholesterol level and immediately followed by administration of the testing medicine. The testing medicine was given orally once a day over 28 days without high cholesterol diet and PTU anymore.

In both methods, before the experiment was started, the total blood cholesterol level of animals was measured as starting normal level. Total blood cholesterol level was observed once a week over 4 weeks. The blood samples were collected from the tail vein. The cholesterol level was

measured by colorimetric method with standard enzymatic reagents. One way analysis of variance was used to evaluate the data.

Human trial: Water extract of *Laetiporus* sp. mycelia was made up as capsules for human trial. Each capsule was filled with 500 mg of dried extract by using a manual capsule maker. Nineteen volunteers were involved for the test over 30 days. Each person was asked to consume one capsule per day after having meal before going to bed. Their total blood cholesterol was measured before having *Laetiporus* sp. capsule. After 30 days of treatment once again their blood cholesterol was measured at a local professional public clinic laboratory. The result of the test was then analysed.

RESULTS

Toxicity effects: *Laetiporus* sp. extract did not cause any toxicity effect on rat as evidenced by the growth pattern and organ index values of the assay animals. Figure 1 shows that the male rat body weight on all doses is not significantly different compared to the body weight on control animal. Like wise, female rat body weight, as shown by Fig. 2 also does not differ significantly between all doses treatment compared to control. In addition, Fig. 3 shows that organ index values of male rat do not differ significantly between all doses and control. The same phenomena also occurred on organ index values of female rat as can be seen on Fig. 4, there is no significant different between all doses and control. Growth pattern of the animal tended to fluctuate, increase during 3-5 days and then decrease on the day 6th then again increased for the following days until reach the peak at day 11th and 12th. Organ index values of male and female animals were ranging as follows: heart 0.34-0.42; lung 0.54-0.65; liver 3.89-5.1; kidney 0.98-1.56; spleen 0.2-0.54; testis 0.55-0.71; ovarium 0.04-0.08; vesica seminalis 0.25-0.5 dan uterus 0.26 and 0.65. All organ indexes are not significantly different between doses treatment compared to control.

Cholesterol inhibition effect on rat: Both doses level of mycelial extracts (55 and 110 mg kg^{-1} b.wt.) and commercial lovastatin at dose 1.8 mg kg^{-1} b.wt. were able to inhibit the increase of cholesterol level in the blood. On the other hand, the control group gave a sharp increase of cholesterol level since the first week from 101.99 to 110.73 mg dL^{-1}.

As a hypercholesterolemic inhibitor, *Laetiporus* sp. mycelial water extract at dose 55 mg kg^{-1} b.wt. could inhibit the increase of cholesterol level by 9.1, 8.2, 18.8 and 7.8% on week 1, 2, 3 and 4, respectively or in average of 11% over 4 weeks. On the other hand, fungal extract at dose 110 mg kg^{-1} b.wt. could inhibit the increasing of cholesterol level by 10.5, 19.8, 28.6 and 17.0% on 1, 2, 3 and 4 week, respectively or in average of 19.0% during 4 weeks. Compared to commercial lovastatin tablet it only could inhibit the blood cholesterol level by 11.1, 12.1, 25.4, 10.0% on 1, 2, 3 and 4 week, respectively or in average of 14.6% over 4 weeks (Table 1).

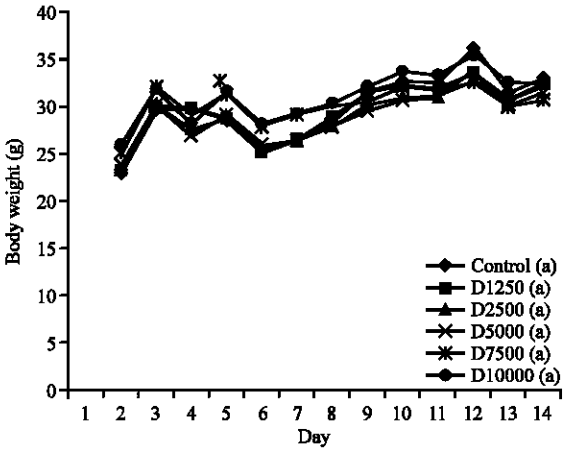

Fig. 1: The effect on growth pattern of male rat after treatment with *Laetiporus* sp. extracts (letters in bracket indicate significance)

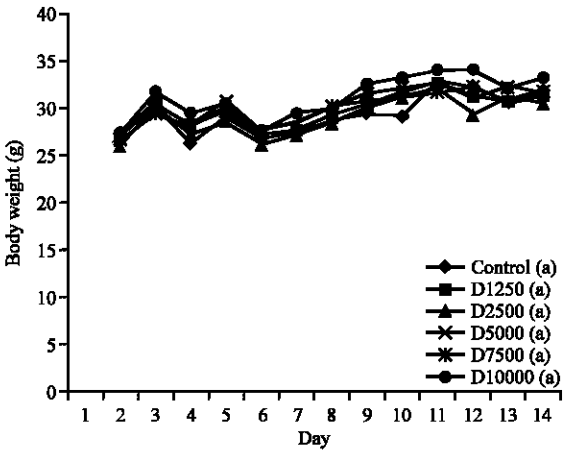

Fig. 2: The effect on growth pattern of female rat after treatment with *Laetiporus* sp. extract (letters in bracket indicate significance)

Cholesterol lowering effect on rat: The result shows the reducing effect of *Laetiporus* sp. extract and commercial lovastatin over 4 weeks. After one week period of time, a significant reduction of blood cholesterol level was

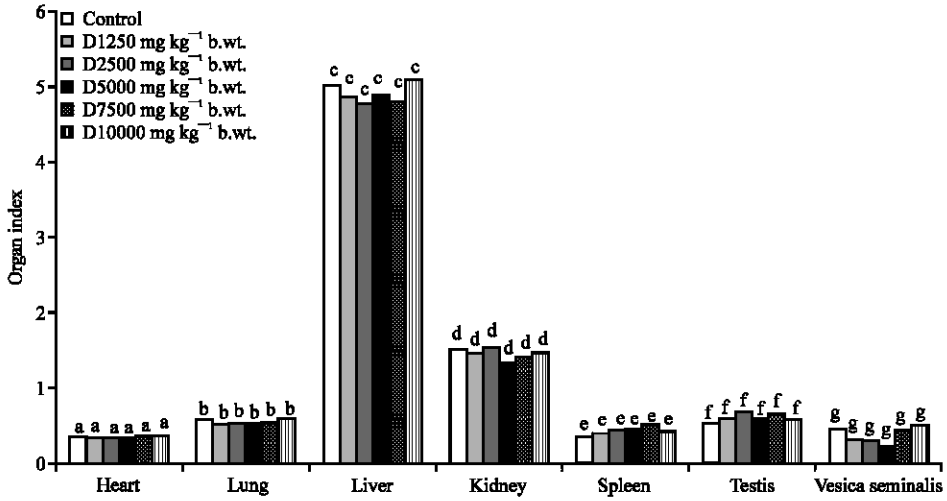

Fig. 3: The effect on male rat organs after treatment with *Laetiporus* sp. extract (letters above the bar indicate significance of data among groups)

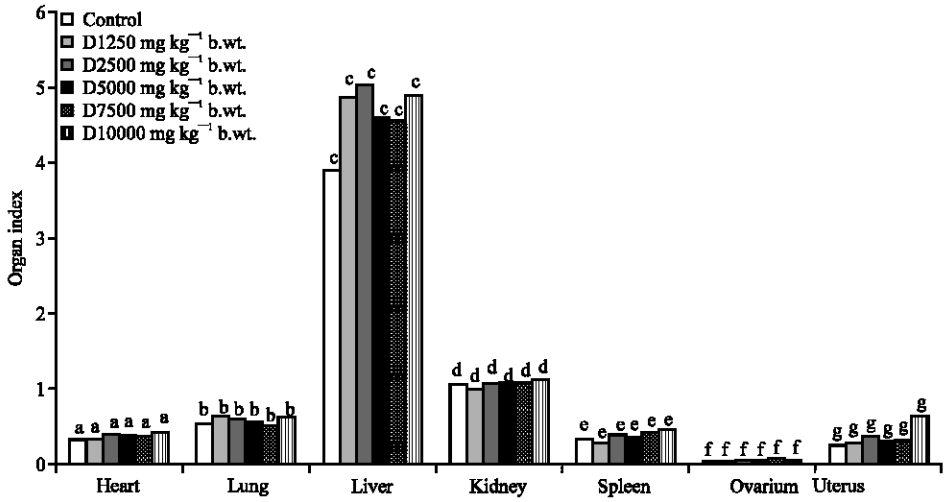

Fig. 4: The effect on female rat organs after treatment with *Laetiporus* sp. extract (letters above the bar indicate significance of data among groups)

achieved by the treatment of fungal extract. The same pattern was also achieved by the commercial lovastatin treatment. The cholesterol level was remain constant for the following 7 days and sharply decreased after 14 days. As a hypercholesterolemic reducer, dose of 110 mg kg^{-1} b.wt. of the mycelial water extract could reduce the blood cholesterol level by 9.4, 15.9, 14.7 and 5.6% on week 1, 2, 3 and 4, respectively or in average of 11.4% over 4 weeks. Compared to commercial lovastatin tablet, it can only reduce the blood cholesterol level average by 5.5% over 4 weeks (Table 2).

Cholesterol lowering effect on human: As can be seen on Fig. 5, fourteen out of nineteen (73.6%) volunteers were

Table 1: Percentage inhibition of blood cholesterol level by *Laetiporus* sp. extracts and commercial lovastatin product compared to control

	Week (%)				
Treatment	1	2	3	4	Average (%)
D55	9.1	8.2	18.8	7.8	11.0
D110	10.5	19.8	28.6	17.0	19.0
Lov 1.8	11.1	12.1	25.4	10.0	14.6

Table 2: Percentage reduction of blood cholesterol level by *Laetiporus* sp. extracts and commercial lovastatin product compared to control

	Week (%)				
Treatment	1	2	3	4	Average (%)
D110	9.4	15.9	14.7	5.6	11.4
Lov 1.8	5.5	17.1	1.6	-2.0	5.5

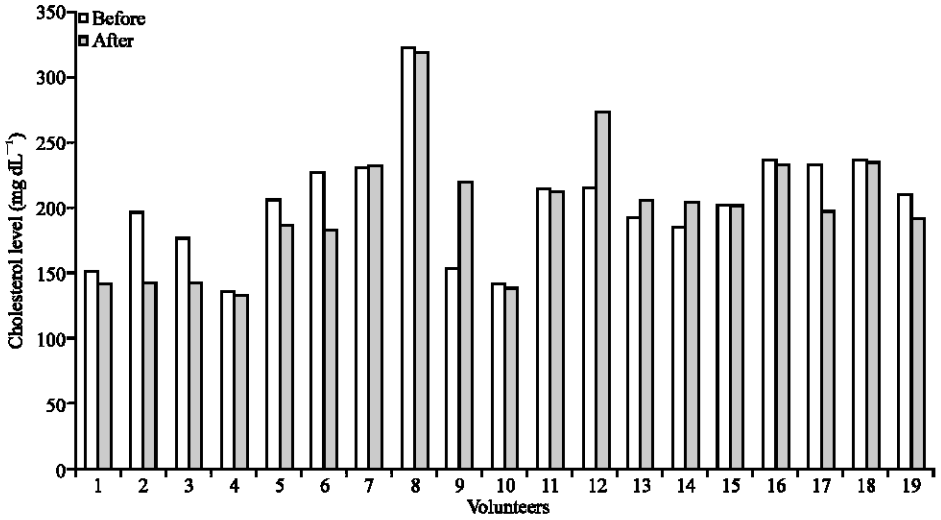

Fig. 5: The effect of *Laetiporus* sp. extract on blood cholesterol level in human volunteers

discovered to have their total blood cholesterol to decrease and 5 out of 19 (26.4%) were increased. The decrease of blood cholesterol varies from 1 up to 45 mg dL^{-1} while the increase varies from 2-66 mg dL^{-1}.

Overall results indicate that water mycelial extract of local Indonesian *Laetiporus* sp. is quite potential for both inhibiting and reducing blood cholesterol level which is almost as effective as commercial anti cholesterol medicine (lovastatin).

DISCUSSION

Anticholesterol agent has been produced commercially from *Aspergillus terreus* (Manzoni *et al*., 1998), *Penicillium citrinum* (Endo *et al*., 1976) and *Monascus purpureus* (Endo, 1979). Unfortunately, *A. terreus*, *P. citrinum* and *M. purpureus* also produce secondary metabolites as mycotoxin which may have side effects to human health. Riba *et al.* (2008) reported that 50% of *Aspergillus terreus* isolated from 85 samples of wheat destined for human consumption in Algeria were Ochratoxin A (OTA) producer (0.01 to 9.35 μg^{-1}. A study in Spain also showed that fourteen isolates (10 *P. verrucosum* and 4 of *P. citrinum*) from total 155 isolates of *Pencillium* sp. were citrinin (CIT) producers (Bragulat *et al*., 2008). In addition, the most frequently isolated genera of moulds from 50 samples of poultry feed in Venezuela, were Aspergillus (36%) and Penicillium (20%). Of these genera, the most frequently isolated species were *A. flavus*, *A. terreus* and *P. citrinum* (Figueroa *et al*., 2009).

Both OTA and CIT are reported to be commonly found in moldy foods in endemic areas of nephropathy, which is associated with urinary tract cancers (Knasmuller *et al*., 2004). Meanwhile, Mayura *et al*. (1984) reported that OTA and CIT, when occur simultaneously, may interact to enhance prenatal toxicity and teratogenicity. Furthermore, extract from submerged *Monascus* cultures was reported to produce mycotoxin which possess embryotoxic and teratogenic activities (Martinkova *et al*., 1995). These informations suggests that micro fungi (*Aspergillus, Penicillium* and *Monascus*) may have negative impacts when used as anti hypercholesterolemial agent. Therefore, safer sources of antihypercholesterolemial agents are required.

Fruiting bodies of edible oyster mushroom (*Pleurotus ostreatus*), were found to contain a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase which was known as lovastatin (Gunde-Cimerman and Cimerman, 1995). In addition, crude methanol extract of other Pleurotus (*P. sapidus* and *P. saca*) were also shown to produce the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor known as mevinolin (Gunde-Cimerman *et al*., 1993).

Our previous results also confirmed the cholesterol lowering and inhibition effects by mycelial hot water extract of *Pleurotus ostreatus* in Wistar rat (Yuli *et al*., 2006). Both mycelial and fruiting body hot water extracts of this mushroom were confirmed to contain lovastatin in other study (Aryantha and Widayanti, 2004). Recently, a local species of Laetiporus was examined and confirmed to produce lovastatin from our previous investigation (Aryantha and Sidharta, 2007). The lowering and inhibition effects of blood cholesterol by this local mushroom apparently were caused by the same substances (lovastatin). In order to prove this hypothesis,

further research by using pure extract of this mushroom needs to be conducted. Up to this stage, the hot water extract of this mushroom was proven to inhibit and to lower blood cholesterol in this study.

Lovastatin was found to be selectively can inhibit hydroxymethyl glutaryl-coenzyme-A (HMG-CoA) reductase, the first enzyme in cholesterol biosynthesis (Endo, 1992). The mechanism involved in controlling plasma cholesterol levels is the reversible inhibition of HMG-CoA reductase by statins due to similarity of the acid form of the statins to HMG-CoA, the natural substrate of the enzymatic reaction (Manzoni and Rollini, 2002). The hypocholesterolemic effect of statins was known to reduce the Very Low-Density Lipoproteins (VLDL) and Low-Density Lipoproteins (LDL) as well as to increase the High-Density Lipoproteins (HDL), with a subsequent reduction of the LDL:HDL-cholesterol ratio. The use of natural statins therefore, can lead to a reduction in hypercholesterolemia related diseases, but the possible interaction of natural statins with other medicine must be taken into account.

There are five types of statin in clinical use i.e. Lovastatin and pravastatin (mevastatin derived) are natural statins of fungal origin, while symvastatin is a semi synthetic lovastatin derivative. Atorvastatin and fluvastatin are fully synthetic statins, derived from mevalonate and pyridine, respectively. Other natural statins which are also fungal origin such as monacolins and dihydromonacolins have also been characterized (Manzoni and Rollini, 2002).

Until recently, there is no information available about anti hypercholesterolemia obtained from *Laetiporus* sp. The most well known species of Laetiporus is *L. sulphureus*. Four strains of *L. sulphureus* are known from nature based on growth cultural conditions and fruit body formation. All strains demonstrated antimicrobial activity against a wide spectrum of Gram-positive and Gram-negative bacteria including methicillin-resistant strain of *Staphylococcus aureus* (MRSA) and glycopeptide-resistant strain of *Leuconostoc mesenteroides*. (Ershova *et al*., 2003). In addition, a new lanostanoid triterpene, 3-oxosulfurenic acid together with three known triterpenes were also isolated from the fruit bodies of *Laetiporus sulphureus*. Cytotoxicity of these compounds and their derivatives was evaluated on HL-60 cells. Further studies revealed that a compound called acetyl eburicoic acid of this mushroom was the most potent apoptosis inducer (Leon *et al*., 2004). This pro-apoptotic stimulus implies possible therapeutic potential and may guide feasibility for more potent statins in anti-cancer strategies (Minichsdorfer and Hohenegger, 2009).

Laetiporus extracts seems to be more effective for inhibiting the cholesterol synthesis rather than reducing cholesterol level in the blood. Nevertheless, cholesterol reducing effect of *Laetiporus* extracts seems to be effective after 2 weeks of treatment. Reducing effect on human blood cholesterol is quite variative among human volunteers. Higher reducing effects occur on some volunteers and low reduction also happened to some volunteers. In contrast, 5 volunteers are in fact their blood cholesterol level increased. This phenomena may occur due to the life style and daily diet of these people may not be appropriate since their diet were not restricted to certain type of food.

To anticipate the negative effects of the *Laetiporus* sp. extract on the health aspects, toxicity evaluation was also conducted on this research. Almost all aspect toxicity being evaluated did not give any different results compared to control treatment. Therefore, *Laetiporus* sp. extract can be considered to be safe as hypercholesterolemia treatment agents.

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REFERENCES

Aryantha, I.P. and S. Widayanti, 2004. The detection of lovastatin on mycelial culture and fruiting body of Oyster mushroom (*Pleurotus ostreatus*). Proceedings of the 4th Seminar Mauritius Institute of Professional Accountants, Oct. 6-7 Bandung, pp: 560-563.

Aryantha, I.P. and M. Sidharta, 2007. Lovastatin production by *Laetiiporus* sp. {Bull. Ex. Fr.} Bond et Sing. in various solid substrates. Proceedings of the Asian Mycological Congress, Dec. 2-6, Penang Malaysia, pp: 58-58.

Bragulat, M.R., E. Martinez, G. Castella and F.J. Cabanes, 2008. Ochratoxin A and citrinin producing species of the genus Penicillium from feedstuffs. Int. J. Food Microbiol., 126: 43-48.

Endo, A., M. Kuroda and K. Tanazawa, 1976. Competitive inhibition of 3-hydroxy-3-methyl glutaryl coenzyme A reductase by ML-236 A and ML-236 B fungal metabolites having hypocholesterolemic activity. FEBS Lett., 72: 323-326.

Endo, A., 1979. Monacolin K, a new hypocholesterolemic agent produced by a *Monascus* species. J. Antibiot., 32: 852-854.

Endo, A., 1992. The discovery and development of HMG-CoA reductase inhibitors. J. Lipid. Res., 33: 1569-1582.

Ershova, E. Iu, O.V. Tikhonova, L.M. Lure, O.V. Efremenkova, O.V. Kamzolkina and I.V. Dudnik, 2003. Antimicrobial activity of *Laetiporus sulphureus* strains grown in submerged culture. Antibiot. Khimioter, 48: 18-22.

Figueroa, S., S. Centeno, M.A. Calvo, A. Rengel and C. Adelantado, 2009. Mycobiota and concentration of ochratoxin a in concentrated poultry feed from Venezuela. Pak. J. Biol. Sci., 12: 589-594.

Gilman, A.G., T.W. Rall, A.S. Nies and P. Taylor, 1990. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th Edn., Pergamon Press, New York.

Gunde-Cimerman, N. and A. Cimerman, 1995. Pleurotus fruiting bodies contain the inhibitor of 3 hydroxy-3-methylglutaryl-coenzyme A reductase lovastatin. Exp. Mycol., 19: 1-6.

Gunde-Cimerman, N., A. Plemenitas and A. Cimerman, 1993. Pleurotus fungi produce mevinolin, an inhibitor of HMG CoA reductase. FEMS Microbiol. Lett., 113: 333-337.

Jeong, S.C., Y.T. Jeong, B.K. Yang, R. Islam and S.R. Koyyalamudi *et al*., 2010. White button mushroom (*Agaricus bisporus*) lowers blood glucose and cholesterol levels in diabetic and hypercholesterolemic rats. Nutr. Res., 30: 49-56.

Knasmuller, S., C. Cavin, A. Chakraborty, F. Darroudi, B.J. Majer, W.W. Huber and V.A. Ehrlich, 2004. Structurally related mycotoxins ochratoxin A, ochratoxin B and citrinin differ in their genotoxic activities and in their mode of action in human-derived liver (HepG2) cells: Implications for risk assessment. Nutr. Cancer, 50: 190-197.

Leon, F., J. Quintana, A. Rivera, F. Estevez and J. Bermejo, 2004. Lanostanoid triterpenes from *Laetiporus sulphureus* and apoptosis induction on HL-60 human myeloid leukemia cells. J. Nat. Prod., 67: 2008-2011.

Lu, X., H. Chen, P. Dong, L. Fu and X. Zhang, 2010. Phytochemical characteristics and hypoglycaemic activity of fraction from mushroom *Inonotus obliquus*. J. Sci. Food Agric., 30: 276-280.

Manzoni, M., M. Rollini, S. Bergomi and V. Cavazzoni, 1998. Production and purification of statins from *Aspergillus terreus* strains. Biotechnol. Tech., 12: 529-532.

Manzoni, M. and M. Rollini, 2002. Biosynthesis and biotechnological production of statins by filamentous fungi. Ann. Applied Microbiol. Biotechnol., 58: 555-564.

Martinkova, L., P. Juzlovga and D. Vesely, 1995. Biological activity of polyketide pigments produced by the fungus *Monascus*. J. Applied Bacteriol., 79: 609-616.

Mayura, K., R. Parker, W.O. Berndt and T.D. Phillips, 1984. Effect of simultaneous prenatal exposure to ochratoxin A and citrinin in the rat. J. Toxicol. Environ. Health, 13: 553-561.

Minichsdorfer, C. and M. Hohenegger, 2009. Autocrine amplification loop in statin induced apoptosis of human melanoma cells. Br. J. Pharmacol. 157: 1278-1290.

Mori, K., C. Kobayashi, S. Tomita, T. Inatomi and M. Ikeda, 2008. Antiatherosclerotic effect of the edible mushrooms *Pleurotus eryngii* (Eringi), *Grifola frondosa* (Maitake) and *Hypsizygus marmoreus* (Bunashimeji) in apolipoprotein E-deficient mice. Nutr. Res., 28: 335-342.

Riba, A., S. Mokrane, F. Mathieu, A. Lebrihi and N. Sabaou, 2008. Mycoflora and ochratoxin A producing strains of *Aspergillus* in Algerian wheat. Int. J. Food Microbiol., 122: 85-92.

Slanc, P., B. Doljak, A. Mlinaric and B. Strukelj, 2004. Screening of wood damaging fungi and inhibitors of pancreatic lipase. Phytother. Res., 18: 758-762.

Yuli, S., A.B. Sutjiatmo and I.P. Aryantha, 2006. Effect of oyster mushroom (*Pleurotus ostreatus*) mycelial water extract on total blood cholesterol level of Wistar female rats. Proceedings of the International Conference on Mathematics and Natural Sciences, Nov. 29-30, Bandung, West Java, pp: 160-160.

Zhang, Z.C., B. Lian, D.M. Huang and F.J. Cui, 2009. Compare activities on regulating lipid-metabolism and reducing oxidative stress of diabetic rats of *Tremella aurantialba* broth's extract (TBE) with its mycelia polysaccharides (TMP). J. Food Sci., 74: 15-21.