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EFFECT OF HOMOGENATES OF AVOCADO PEAR (*PERSEA AMERICANA*) SEEDS AND FLUTED PUMPKIN (*TELFAIRIA OCCIDENTALIS*) LEAVES CO-ADMINISTERED WITH ANTI-TUBERCULOSIS DRUGS ON LIVER ENZYMES OF ALBINO RATS

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ABSTRACT

This study evaluated the effects of aqueous homogenates of avocado pear (Persea americana) seeds and fluted pumpkin (Telfairia occidentalis) leaves co-administered with anti-tuberculosis drug on liver enzymes of albino rats. Twenty (20) albino rats were divided into five (5) groups (of four rats each) designated as I, II, III, IV and V (which is the normal control). A dose of 5.14mg/kg body weight of a first line anti-tuberculosis drug (a combination of isoniazid, rifampicin, pyrazinamide and ethambutol) was administered orally to two (2) rats in group I, II, III, and IV for seven (7) days and the remaining two rats in each group for fourteen (14) days. The homogenates of avocado pear seeds (at a dose of 250mg/kg body weight), fluted pumpkin leaves (at a dose of 250mg/kg BW) and a mixture of avocado pear seeds and fluted pumpkin leaves (at a dose of 250mg/kg BW, and 125mg/kg BW respectively) were co-administered with the anti-TB drug to groups II, III and IV respectively. Group I rats served as the positive control (i.e. treated with only 5.14mg/kg BW of anti-TB drug). The results indicated that the activities of serum AST, ALT and ALP were significantly higher (P<0.05) in rats administered with 5.14 mg/kg BW first line anti-TB drugs only when compared with that of the rats co-administered with the same anti-TB drug and 250mg/kg BW plant homogenates (avocado pear seeds, fluted pumpkin leave, and a combination of the two homogenates). The mean serum AST, ALT and ALP activities were found to have decrease (P<0.05) in groups II, III, and IV rats from the beginning to the end of the treatment periods. Similarly, mean serum activities of AST, ALT and ALP in group III rats decreased (P<0.05) significantly when compared with that of group II rats. Moreover, the serum activities of these enzymes were significantly lower (P<0.05) in group V rats compared to that of groups II and III rats. The rise in the mean serum activities of liver enzymes in group I rats when compared to that of group V rats indicated that the anti-TB drug is hepatotoxic. The findings of this research work predicts that the aqueous homogenates of both avocado pear seeds and fluted pumpkin leaves have hepatoprotective abilities but, the combination of these plant parts shows more hepatoprotective function (i. e. exhibits synergy).

Key words: Avocado pear, fluted pumpkin, homogenates, anti-tuberculosis, isoniazid.

INTRODUCTION

The liver is of vital importance in intermediary metabolism and in detoxification and elimination of toxic substances. It is often affected by a multitude of environmental pollutants and drugs, all of which place a burden on this vital organ, causing damage and weaken it, eventually leading to diseases like hepatitis or cirrhosis (Krishna *et al*., 2012). Liver disease can occur due to tuberculosis and its treatment with various anti-tuberculosis drugs may precipitate hepatic injury. Similarly, patients with chronic liver disease may develop tuberculosis and pose special management problems (Sonika and Kar, 2012).

Drug-induced liver toxicity is a common cause of liver injury and it accounts for approximately one-half of the cases of acute liver failure which mimics all forms of acute and chronic liver disease (Neil, 2011). Due to toxicity of this kind among others, it is necessary to continue searching for new and if possible, more efficacious management. The vast reserves of phytotherapy may just as well be an ideal area of interest in this regard. For thousands of years, plants have played a significant role in maintaining human health and improving the quality of life. In particular, herbs have been used for centuries as food and medicine (Mahadeva and Bizuneh, 2011). Green leafy vegetables are particularly important in promoting health because of their rich sources of phytonutrients (Gupta and Jain, 2010).

Persea americana also known as avocado, alligator pear or *aguacate* is a tree native to central Mexico (Chen *et al*., 2008). Avocado contains a variety of vitamins, minerals and phytochemicals such as lutein, phenolic antioxidants and phytosterols associated with numerous potential health benefits (Wu *et al*., 2004). Avocado has traditionally been used due to its anti-bacterial, anti-fungal, hypotensive, anti-inflammatory and immune-enhancing effects (Adeyemi *et al*., 2002).

Although the avocado seed represents a considerable percentage of the total fruit, scientific research on the phytochemistry and biological effects of avocado seeds is in the nascent stage. Currently, the seed represents an under- utilized resource and a waste issue for avocado processors. Studies have shown that avocado seed has more than 70% of the antioxidants found in the whole avocado fruit, and its seed oil is full of antioxidants, lowers blood cholesterol level, and helps fight off disease (Paul *et al*., 2011).

Telfairia occidentalis also called fluted pumpkin or ugu leaf in Igbo dialect occurs in the forest zone of west and central Africa, most frequently in Benin, Nigeria and Cameroon. It is a popular vegetable all over Nigeria (Badifu and Ogunsua, 1991). Fluted pumpkin contains nutrients such as proteins, carbohydrates, vitamins, minerals and fiber (Fasuyi, 2006). It also contains oxalates, saponins, glycosides, flavonoids, alkaloids and resins (Akubue *et al*., 1980). Aqueous extract of fluted pumpkin has been reported to increase hematological parameters (Alada, 2000), and hsa also been shown to be hepato protective against garlic induced oxidative stress (Olorunfemi *et al*., 2010). Its ethanolic extracts have demonstrated hypoglycaemic properties both in normoglycaemic and alloxan-induced diabetic rats (Nwozo *et al*., 2004).

Drug-induced hepatotoxicity is a potentially serious adverse effect of anti-tuberculosis regimen (Baghaei *et al*., 2010). Furthermore, research on non-toxic and highly effective new compounds for treating tuberculosis or an effective vaccine conferring sustained protective immunity is not yet known (Nasiru *et al*., 2012). Nowadays, plants provide an alternative strategy in search for new drugs. Avocado pear seeds (Paul, 2011) as well as fluted pumpkin leaves (Alada, 2000) have been reported in traditional medicine to possess protective and therapeutic properties. Investigating these plant products to access their effects on the damage done to the liver by the anti-tuberculosis drugs will be of great importance.

MATERIALS AND METHODS

Plant Collection and Preparation

The fresh leaves of fluted pumpkin were purchased from Yankura market, Sabon-Gari Kano State. The leaves were air dried at room temperature, pulverized using laboratory pestle and mortar, and sieved to get the finest powder. Fresh avocado pear fruits were harvested from its natural habitat at Ufuma, Orumba North Local Government Area, Anambra State. The seeds were removed from the pulp, de-shelled, chopped into smaller pieces, air dried at room temperature, pulverized using laboratory pestle and sieved to get the finest powder.

Preparation of Plant Homogenates

About 25mg/ml of fluted pumpkin leaf and avocado pear seed homogenates were separately prepared by macerating 2.5g of powdered fluted pumpkin leaf and avocado pear seed in 100ml of distilled water in separate air tight bottle. Then, 12.5mg/ml each of fluted pumpkin leaf and avocado pear seed homogenate were also prepared in another different air tight bottle by macerating 1.25g each of powdered fluted pumpkin leaf and avocado pear seed in 100ml of distilled water. These were kept at room temperature until they were reconstituted for administration.

Anti-tuberculosis drug

The first-line anti-tuberculosis drug (tablet) was purchased from a drug Market at Igbo Road, Sabon-Gari, Kano. Each film coated tablet known as Akurit-4, contains: Rifampicin U.S.P 150mg**,** Isoniazid U.S.P 75mg**,** Pyrazinamide U.S.P 400mg**,** Ethanbutol hydrochloride U.S.P 275mg. This drug was manufactured by Sandoz private limited.

The drug was stored in a cool and dry place protected from light and excessive humidity for subsequent preparation during the study.

Experimental animals and design

A total of twenty (20) albino rats weighing about 100g each were obtained from animal house of Physiology Department, Bayero University, Kano and kept in the animal house of Biological Sciences Department, Bayero University, Kano. The rats were kept under the same atmospheric conditions and fed with animal feed and water for three (3) weeks to get acclimatized. The rats were randomly assigned to 5 experimental groups of 4 rats each as shown below:-

Group I: Served as positive control and were administered with anti-tuberculosis drugs (51.4mg/kg) once daily.

Group II: Received avocado pear seed homogenate (250mg/kg) co-administered with anti-tuberculosis drugs (5.14mg/kg) once daily.

Group III: Received fluted pumpkin leaf homogenate (250mg/kg) co-administered with anti-tuberculosis drugs (5.14mg/kg) once daily.

Group IV: Received homogenate of both avocado pear seed and fluted pumpkin leaf (250mg/kg, i.e.125mg/kg each) co-administered with anti-tuberculosis drugs (5.14mg/kg) once daily.

Group V: Served as negative control and were administered with distilled water (1ml/kg) once daily.

At the end of 7^{th} day of the treatment, two rats were taken from each group, weighed and sacrificed; this was also done to the remaining two rats in each group at the end of 14^{th} day of treatment. The rats were sacrificed by cervical decapitation, and blood taken for analysis of biochemical parameters (aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase).

Biochemical assays

Serum alanine aminotransferase and serum aspartate aminotransferase were determined as described by Reitman and Frankel, 1957; while serum alkaline phosphatase was determined as described by Englehardt *et al*., (1970).

STATISTICAL ANALYSIS

The data was statistically analyzed using ANOVA and multiple comparisons test, with GraphPad Instat3 Software (2000) version 3.05 by GraphPad Inc.

RESULTS

The results of serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) analysed in albino rats, given homogenates of *Telfairia occidentalis* (fluted pumpkin) leaves, *Persea americana* (avocado pear) seeds and a mixture of both co-administered with anti-tuberculosis (anti-TB) drugs for seven (7) days and fourteen (14) days are shown in tables 1 and 2.

Table 1. Mean serum AST, ALT and ALP activities in experimental rats after seven days of treatment.

Groups (n=2)	AST (U/L)	ALT (U/L)	ALP (U/L)
I (Positive control, anti-TB)	$47.00 \pm 0.28^{a,b,c,d}$	$54.10 \pm 2.90^{h,i,j,k}$	$86.90 \pm 0.21^{o,p,q,r}$
II (Avocado pear seed, APS)	$38.50 \pm 3.54^{a,e,f}$	$40.40 \pm 3.68^{h,l,m}$	$76.40 \pm 0.14^{o,s,t}$
III (Fluted pumpkin leaves, FPL)	$27.20 \pm 0.21^{b,e,g}$	$23.40 \pm 2.33^{i,l,n}$	$57.00 \pm 0.71^{p,s,u}$
IV (APS and FPL)	$17.00 \pm 0.50^{c,f,g}$	$15.80 \pm 0.00^{j,m,n}$	$38.60 \pm 0.57^{q,t,u}$
V (Negative control)	10.20 ± 0.21^{d}	10.00 ± 0.13^{k}	33.00 ± 0.07^{r}

Values are mean ± standard deviation.
Values in the same column having the same superscript are significantly different (P<0.05).

From table 1 above, there is significant difference (P<0.05) between the serum levels of AST, ALT and ALP of group I (positive control group) compared to groups (groups II, III, IV and V respectively). There is also significant difference (P<0.05) in the serum AST and ALP levels between group V (negative control group) and groups II, III and IV respectively. The serum ALT level of groups II and III were significantly different at P<0.05 when compared with that of the negative control group, whereas the ALT level of group IV showed no significant difference (P>0.05) when compared with that of the negative control group.

Table 2. Mean serum AST, ALT and ALP activities in experimental rats after fourteen days of treatment.

Groups (n=2)	AST (U/L)	ALT (U/L)	ALP (U/L)
I (Positive control, anti-TB)	$56.30 \pm 1.49^{a,b,c,d}$	$56.90 \pm 014^{h,i,j,k}$	$96.80 \pm 0.00^{o,p,q,r}$
II (Avocado pear seed, APS)	$33.30 \pm 0.21^{a,e,f}$	$43.90 \pm 0.14^{h,l,m}$	$70.40 \pm 0.64^{o,s,t}$
III (Fluted pumpkin leaves, FPL)	$19.50 \pm 0.71^{b,e,g}$	$18.10 \pm 0.50^{i,l,n}$	$55.20 \pm 0.35^{p,s,u}$
IV (APS and FPL)	$14.50 \pm 2.12^{c,f,g}$	$13.20 \pm 0.21^{j,m,n}$	$36.40 \pm 0.23^{q,t,u}$
V (Negative control)	11.20 ± 0.21^{d}	09.68 ± 0.11^{k}	34.40 ± 0.14^{r}

Values are mean ± standard deviation.
Values in the same column having the same superscript are significantly different (P<0.05).

From table 2 above, there is significant difference (P<0.05) in the serum levels of AST, ALT and ALP of groups II, III, IV and V when compared with that of group I (positive control group). There is also a significant difference (P<0.05) in the serum level of ALT and ALP of groups II, III and IV when compared with that of group V. The serum level of AST of groups II and III are significantly different at P<0.05 when compared with that of the negative control group, but the serum AST level of group IV showed no significant difference at P>0.05 when compared with that of the negative control group.

DISCUSSION

From the results obtained, there is significant difference (P<0.05) between the serum levels of AST, ALT and ALP of group 1 (positive control) and that of group V (negative control) (Tables 1 and 2), indicating that the first line anti-tuberculosis (anti-TB) drug have induced liver damage after seven days of treatment (Table 1). Baghaei *et al*. (2010), Sude *et al*. (2008) and Tostmann *et al*. (2008) had reported that drug induced liver damage is an adverse effect of anti-tuberculosis drugs. The reactive oxygen species generated from the biotransformation of anti-tuberculosis drugs may have reacted with cellular components in the liver, and caused liver injury resulting in impairment of liver functions (Tasduq *et al*., 2005). Anti-tuberculosis drugs may have also damaged mitochondria, an intracellular organelle that produces energy, whose dysfunction releases excessive amount of oxidants which in turn injures hepatic cells (Shah, 1999). Studies have indicated the existence of a strong correlation between hepatic injury and oxidative stress in experimental animals treated with anti-tuberculosis drugs (Pal *et al*., 2006; Rana *et al*., 2006). Other studies have shown that anti-tuberculosis drugs generally act as inducers of hepatic cytochrome P_{450} enzymes (Trevor *et al*., 2004; Vuilleumier *et al*., 2006).

The findings of this work also shows that *Percia americana and Telfairia occidentalis* homogenates may be hepatoprotective against anti-TB induced liver damage when the serum activities of AST, ALT and ALT in groups II, III and IV (groups given plants homogenates co-administered with the anti-tuberculosis drugs) where compared with those of group I (positive control group which received anti-TB drugs only) (Tables 1 and 2). This finding conforms to the findings of Emeka and Obidoa (2009) and Kayode *et al*. (2010) on the hepatoprotective effects of fluted pumpkin leaves in experimental rats. It is also consistent with the findings of Imafidon (2010) on the anti hepatotoxic effects of avocado pear seeds in rats. Inhibition of CYP2E1 isozyme and antioxidant actions seems to be the common mechanism of action of herbal drugs (Pal *et al*., 2006; Tasduq *et al*., 2005).Studies have shown that avocado seed has more than 70% of the antioxidant found in the whole avocado, and its seed oil is full of antioxidant (Paul, 2011). Some studies have shown that fluted pumpkin leaves are rich in antioxidants such as ascorbic acid and phenolics (Oboh, 2005).

Other studies have shown that antioxidants in avocado pear fight off damage from free radicals, thereby protecting the organs and tissues from damage over time. Also, fluted pumpkin leaf extracts have been found to suppress or prevent production of free radicals and scavenge already produced free radicals, lower lipid peroxidation status and elevates antioxidant enzymes both in vitro and in vivo (Adaramoye *et al*., 2007; Kayode *et al*., 2009; Kayode *et al*., 2010).

This study also shows that the serum AST, ALT and ALP levels of rats in group III (given homogenate of fluted pumpkin leaves co-administered with anti-TB drugs) are significantly lower ($P<0.05$) when compared to that of the rats in group II (given homogenate of avocado pear seeds co-administered with anti-TB drugs) (Tables 1 and 2), suggesting that fluted pumpkin leaves are more hepatoprotective than avocado pear seeds. This may be due to the presence of high antioxidant (e.g. polyphenols) content in fluted pumpkin leaves (Oboh *et al*., 2006) higher than that of avocado pear seeds. The serum activities of the enzymes of rats in group IV are significantly ($P<0.05$) lower compared to those of groups II and III. This predicts that the mixture of *Percia americana and Telfairia occidentalis* homogenates may be more hepatoprotective than individual plant homogenate.

However, no significant difference ($P>0.05$) was recorded in the serum ALT and AST levels (table 1 and 2) of rats in group IV when compared with those of group V rats. This might be as a result of synergistic effects of co-administration of both plants homogenates. Serum activities of AST, ALT and ALP in rats of groups II, III, and IV are significantly lower after 14 days of treatment when compared to 7 days treat1ment. This shows the hepatoprotective effects of these plants homogenates depends on the duration of the treatment.

CONCLUSION

This study demonstrated the hepatoprotective ability of fluted pumpkin leaves and avocado pear seed against anti-TB drugs induced hepatotoxicity in rats. Though fluted pumpkin leaves proved to be more effective than avocado pear seeds, a combination of both shows synergy.

REFERENCES

Adaramoye O.A., Achem J., Akintayo O.O. and Fafunso M.A., (2007). Hypolipidaemic Adeyemi O.O., Okpo S.O. and Ogunti O.O. (2002). Analgesic and anti-inflammatory effects of the aqueous extract of leaves of *Persea americanamill (lauraceae)*. *Fitoterapia*.**73**(5):375-380.

Akubue P.I., Kar A. and Nnachetta F.N. (1980). Toxicity of extracts of roots and leaves of *Telfairia occidentalis*. *Planta Med*. **38**:339-343

Alada A.R.A. (2000). The haematological effect of *Telfairia occidentalis* diet preparation. *Afr. J. Biomedical Res*.**3**:185-186.

Badifu G.I.O and Ogunsua, A.O. (1991). Chemical Composition of Kernels from some species of *Cucurbitaceae* grown in Nigeria. *Plant foods Human Nutr*. **41**:35-44.

Baghaei P., Tabarsi P., Chitsaz E., Saleh M., Marjani M., Shemirani S., Valiollah M.P., Kazempour M., Farnia P., Fahimi F., Mansouri D. and Masjedi M. (2010). Incidence, clinical and epidemiological risk factor, and outcome of drug-induced hepatitis due to antituberculous agents in new tuberculosis cases. *AM. J. Ther*. **17**:17-22.

Chen H., Morell P.L., Ashworth V.E.T.M., Cruz M. and Clegg M.T. (2008). Tracing the geographic origins of major avocado cultivars. *Journal of Heredity.* **100**(1):56-65.

Emeka E. J. I. and Obidoa O. (2009). Some biochemical, haematological and histological responses to a long term consumption of *TelfairiaOccidentalis*-supplemented diet in rats. *Pak. J. Nutr*. **8**:1199-1203.

Englehardt A., Adefolaju G., Enaibe B. and Alabi O. (1970). Acid and Alkaline Phosphatase activities in the small intestine of the rat (*Rattus norvegicus*), Bat (*Eidolon helvum*) and Pangoli (*Manis tricuspis*).*Aerztl Labor*. **16**:42.

Fasuyi A.O. (2006). Nutritional potentials of some tropical vegetable leaf meals: chemical characterization and functional properties. *Afr. J. Biotech*. **5**:49-53.

Gupta N. and Jain U.K. (2010). Prominent wound healing properties of indigenous medicines. *Journal of Natural Pharmaceuticals*. **1**(1):2–13.

Imafidon K.E. (2010). Liver Function Status of Hypertensive and Normotensive Rats Administered *Persea americana*Mill*.* (avocado) seeds*. Academic Journal of Plant Sciences.* **3**(3):130-133.

Kayode O.T., Kayode A.A. and Odetola A.A. (2009). Therapeutic effect of *Telfairia occidentalison* protein energy malnutrition-induced liver damage. *Res. J. Med. Plant*.**3**:80-92.

Kayode A.A.A., Kayode O.T. and Odetola A.A. (2010). *Telfairia occidentalis* ameliorates oxidative brain damage in malnourished rats. *Int. J. Biol. Chem*. **4**:10-18.

Krishna C.D.A., Reddy C.S. and Reddy A.M. (2012). Hepatoprotective effect of biherbal ethanolic extract against paracetamol-induced hepatitis damage in albino rat. *J. Ayurveda Integr. Med.* **3**(4):198-203.

Mahadeva U.R. and Bizuneh A. (2011). Remnant B-Cell Stimulant and Anti-oxidative effects of *Persea Americana* Fruit extract studied in Rats introduced into Streptozotocin-induced Hyperglycaemic State. *African Journal of Traditional, Complementary and Alternative Medicines (AJTCAM)*. **8**(3):210-217.

Nasiru A., Hafsat I.G., Mohammad M.M., and Sabo A.A. (2012). Hepatoprotective Effect of Garlic homogenate co-administered with anti-tuberculosis drugs in rat liver enzymes. *International Journal of Bioscience, Biochemistry and Bioinformatic.***2**:5.

Neil, K. (2011). Clinical Infectious Diseases. *Oxford Journals*. **38**(2):544-548.

Nwozo S.O., Adaramoye O.A. and Ajaiyeoba E.O. (2004). Antidiabetic and hypolipidemia studies of *Telfairia Occidentalis* on alloxan induced diabetic rabbit. *Nig. J. Nat. prod. med*. **8**:45-47.

Oboh G. (2005). Hepatoprotective property of ethanolic and aqueous extracts of fluted pumpkin (*Telfairia occidentalis*) leaves against garlic-induced oxidative stress. *J. Med. Food*. **8**(4):560-563.

Oboh G., Nwanna E.E. and Elusiyan C.A. (2006). Antioxidant and antimicrobial properties of *Telfairia occidentalis* (Fluted pumpkin) leaf extracts. *J. Pharmacol. Toxicol.* **1**:167-175.

Olorunfemi A.E., Patrick E., Eyong U.E.Y., Emem U. and Oladoja A. (2010). Comparative Hypoglycaemic effects of ethanolic and aqueous extracts of the leaf and seed of *Telfairia Occidentalis*. *Turk. J. Pharm. Sci*. **7**(1):29-34.

Pal. K., Vaiphei K., Sikander A., Singh K. and Rana, S.V. (2006). Effect of garlic on isoniazid and rifampicin-induced hepatic injury in rats. *World Gastroenterol*. **12**:636-639.

Paul R., Kulkarni P. and Ganesh N. (2011). Avocado fruit (*Persea americana* mill) exhibits Chemoprotective potentiality against Cyclophosphamide induced genotoxicity in human lymphocyte culture. *J. Exp. Ther. Oncol*. **9**(3):221-30.

Rana S.V., Attri S., Vaiphei K., Pal R., Attri A., Sodhi C.P., Kanwar S. and Singh K., (2006). Role of N-acetylcysteine in rifampicin-induced hepatic injury of young rats. *World Gastroenterol*. **12**:287-291.

Reitman S., Frankel S. and Amer J. (1957). Standardization of clinical enzyme assays: a reference method for aspartate and alanine transaminases. *J Clinical pathology.* 1st Edition. **28**:56.

Shah R.R. (1999). Drug induced hepatotoxicity: Pharmacokinetic perspectives and strategies for risk reduction. *Adverse drug reactions and toxicological reviews*.**18**(4):181-233.

Sonika U. and Kar P. (2012). Tuberculosis and liver disease: Management issues *Trop. Gastroenterol.* **33**(2):102–106.

Sude E., Fikriye U. and Fikret V.I. (2008). Silymarin protects Liver against toxic effects of anti-tuberculosis drugs in experimental animals. *Nutr. Metab. (Lond).***15**:18.

Tasduq S.A., Peerzada K., Koul S., Bhat R., and Johri R.K. (2005). Biochemical manifestations of anti-tuberculosis drug induced hepatotoxicity and the effect of Silymarin. *Hepatol. Res*. **31**:132-135.

Tostmann A., Boeree M.J., Aarnoutse R.E., Lange W.C., Van der Ven A.J., Kisoga R., Semvua H. and Gibson S.K. (2008). Antituberculosis drug induced hepatotoxicity. *J. Gastroenterol Hepato*. **23**:192-202.

Trevor A., Katzung B. and Masters S. (2004). Katzung and Trevor's pharmacology. MCGraw – Hills. 3rd Edition. Pp. 53-59.

Vuilleumier N., Rossier M. F., Chiappe A., Degoumois F., Dayer P., Mermillod B., Nicod L., Desmeules J. J. and Hochstrasser D. (2006). CYP2E1 genotype and isoniazid-induced hepatotoxicity in patient treated for latent tuberculosis *Eur J Clin Pharmacol*., vol. **62**, pp. 423–429.

Wu X., Gu L., Holden J., Haytowitz D.B., Gebhardt S.E., Beecher G. and Prior R.L. (2004). Development of a database for total antioxidant capacity in foods: a preliminary study. *J. Food Comp. and Anal*. **17**:407–422.