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Haematopoietic Potential of Rice Husk Extract in Codeine Administered Male Wistar Rats

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Abstract

Oryza sativa (rice) is a widely consumed staple grain with significant amount of fibre, carbohydrate, and trace amount of other biomolecules such as minerals and vitamins. Thus, it's a good energy source. The pre-clinical and clinical investigations of rice hull has revealed its numerous health benefits. Utilization of rice products as dietary supplements, additives and pharmacological adjuvants has become a global trend. Rice husk (RH), is a by-product of rice milling generated in tremendous quantity. Considering the global trend in codeine consumption especially by the youths, this study adopted codeine as a drug of abuse as against its therapeutic use as an analgesic. The study explored the haematopoietic potential of rice husk methanol extract (RHME) in codeine-administered male Wistar rats. A total of thirty-six (36) rats weighing between 100-110g were procured and assembled into 6 groups of 6 rats. Group I was the negative control (NC), Group II received codeine at 10mg/kg body weight, Group III received 10mg/kg body weight of RHME, while Groups IV, V, and VI received codeine with RHME concurrently but at three different concentrations of 250, 500, and 1000mg/kg respectively. After 30 days of treatment, blood samples of the specimens were subjected to haematological assay. From the assessment, codeine administration significantly decreased the haematological indices (PCV, haemoglobin, RBC, WBC, platelets, neutrophil, eosinophil, lymphocyte and monocyte), while RHME administration significantly upregulated the altered blood parameters concentration. Thus, RH showed haematopoietic efficacy and should be considered a possible therapeutic for prevention and/or management of anaemia as well as boosting of key haematology indices.

Keywords: *Anaemia, Codeine-toxicity, Haematology, Haematopoietic, Rice husk extract*

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Introduction

Over 50% of people of the world populace consume rice as primary/staple food (Muthayya *et al*., 2014). According to estimates from the United States Department of Agriculture (USDA), about 483.1 million tons of rice were harvested globally in 2017. According to Park *et al*. (2019), a complete rice grain consists of 20% rice hulls, 72% endosperm, and 8% rice bran. As per Nenadis *et al*. (2013), the hulls generated from the milling process pose a significant disposal challenge for the milling sector. Until recently, the only application of this agro-waste is its use as animal chow in the poultry and animal husbandry industries (Vadivel & Brindha, 2015), while the bulk are discharged as waste (Pode, 2016). As a good source of dietary fibre, rice contains arabinoxylans, -d-glucans, rhamnose, xylose, galactose, mannose, and glucose, while cellulose hemicellulose, insoluble -glucan, and arabinoxylans make up insoluble dietary fibre (Fernando, 2013). Furthermore, has shown to possess several antioxidant compounds, which are essential for good health (Burlando & Cornara, 2014; Goufo & Trindade, 2014).

Globally, several reports have posited the nutritional value of various rice cultivars and the existence of variety of bioactive chemicals in rice. According to Burlando & Cornara (2014), rice contains 80% carbs, 7-8% protein, 3% fat, 3% fiber, minerals and many other bioactive substances. Burlando & Cornara (2014) also reported the presence of hydroxybenzoic acid (such as gallic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, syringic acid, and hydroxycinnamic acid) and hydroxycinnamic acid (which includes caffeic acid, chlorogenic acid, ferulic acid, sinapic acid, and p-coumaric acid) in the peel, hull, and shell of rice. Asper Wahyuni *et al*. (2016), ethanolic extracts of black rice bran and rice hull improved liver glucose metabolism, stimulated insulin levels, inhibited -glucosidase, and promoted the regeneration of pancreatic beta cells that were compromised by oxidative stress in alloxan-induced diabetic rats and mice. These effects significantly reduced blood sugar level. In type 2 diabetic patients, lowered blood lipid profiles, serum cholesterol, glycated haemoglobin, and LDL

including enhanced insulin profile and blood adiponectin are recorded (Lai *et al*., 2012).

The cytotoxic and antimutagenic impact of rice husk has also been studied. According to Nilnumkhum, *et al*. (2017), rice husk-derived vanillic acid produced significant antimutagenicity activity against Aflatoxin B1 -induced mutagenesis in bacterial and immature models. Momilactone B, a compound isolated from rice hull, also demonstrated potent cytotoxic effects against the HT-29 and SW620 human colon cancer cells (Kim *et al*., 2007). Codeine (3-methylmorphine) still assumes of the most widely used opiates in the world due to its analgesic, antitussive, and antidiarrheal proclivity (Carney *et al*., 2018). Despite its use as a mild opiate, it also has the potential for abuse, dependency, and misuse (Nielsen, S., & Van Hout, 2015). Nephrotoxicity, hepatotoxicity, neurotoxicity, lung damage, and stomach ulcers has been reported from long-term exposure to codeine medications and abuse (Van Hout, 2014). Drug addiction may be considered a chronic and relapsing condition that makes its victim dependent on it and comes with severe, detrimental effects. Leukocytosis, or elevated WBC, has been reported as indication of a metabolic condition with a risk factor for several illnesses including leukemia (Jiang *et al*., 2014; Riley *et al*., 2015). In early stages of substance abuse, euphoria and happy emotions or lessens unpleasant emotions like grief, pain, and anguish are common. According to Jordi & Magi (2003), consistent usage triggers adaptive nervous system alterations, which may lead to tolerance, physical dependency, sensitization, craving, and recidivism. Although abuse of opioid drugs in Nigeria and other developing countries especially in Africa is becoming alarming, there is little documented evidence on the likely side effects of the misuse of codeine, and as such, there is no sufficient scientific knowledge on its implications in the haematological indices of abused individuals. Despite being used extensively for many years, codeine and other opioids have not been associated with blood profile abnormalities throughout therapy, nor have there been any compelling instances of idiosyncratic acute, clinically referred harm that can be directly associated to its use. This study investigated codeine as a drug and not as an analgesic which contain the antitussive, euphoria effect or pain suppressants that are common when opioids are abused. This work examined the impact of oral administration and repeated exposure of male young Wistar rats to codeine on haematological indices.

Materials and Methods

Procurement of Experimental Animals

A total of thirty-six (36) male Wistar albino rats with an average weight of 100-110g were used for this experiment. They were procured and housed in the animal house of the Department of Pharmacology, University of Port Harcourt, Rivers State. The animals were left for 1 week to accustom to the laboratory conditions during which they were administered only rat chow and clean water and were later grouped into six groups of six animals per group.

Collection of Plant Sample

Rice husks was harvested from a local rice mill at Awgu in Enugu State, South-East Nigeria.

Preparation of Plant Extract

The rice husks were pulverized and filtered through a 4.8mm mesh sieve. The powdered rice husk sample was weighed and subjected to extraction using a Soxhlet extractor apparatus and methanol as the extraction solvent. The resultant extract was concentrated at 40 - 45^{o}C using a rotary vacuum evaporator with an ultra-cryostat. The brown paste semi solid obtained was stored in an airtight container in the refrigerator at 4^{o}C till usage. Different concentrations of the extracts were obtained by weighing appropriate measure of the extract, which were diluted with distilled water before oral administration.

Groupings of Experimental Animals

The animals were selected randomly and grouped into six groups of six rats per group as follows:

Group I: Negative control rats that received only chow and distilled water.
Group II: Codeine control rats that received 10mg/kg body weight of codeine.
Group III: Rice husk extract control rats that received 500mg/kg body weight of the extract.
Groups IV: Rats received 10mg/kg codeine alongside 250mg/kg RHE
Groups V: Rats received 10mg/kg codeine alongside 500mg/kg RHE
Groups VI: Rats received 10mg/kg codeine alongside 1,000mg/kg RHE

Treatments were done daily via oral administration that lasted for a period of 30 days. After 30 days of treatment, the animals were fasted overnight, and blood samples collected via cardiac puncture under light diethyl ether anaesthesia. Blood samples were collected with ethylene diamine tetra-acetic acid (EDTA) sample bottles for the haematology assay.

Method of Analysis

Haematological parameters (Packed cell volume (PCV), haemoglobin (Hb) concentration, red blood count (RBC), white blood count (WBC), platelet count, neutrophils (Neu.), lymphocytes (Lym.), eosinophils (Eos.), and monocytes (Mon.)), were determined using a MINDRAY auto-haematology analyser. The blood sample was mixed with a sample mixer for 2-5 minutes, after which an aliquot of the samples was injected into the analyser. The haematological parameters to be analysed were selected and the machine was allowed to run for 2-3 minutes after which the results were displayed and printed.

Statistical analysis

All data were subjected to statistical analysis. Values were reported as Mean ± standard deviation (SD), while Duncan Test of One-way ANOVA was used to test for significant differences between groups. The results were considered significant at p-values of less than 0.05, that is, at 95% confidence level ($p \leq 0.05$).

Ethical approval

Ethical approval was obtained from University of Port Harcourt Research Ethics Committee, with Reference Number (UPH/CEREMAD/REC/MM79/026).

Results

From the result presented in Table 1, the PCV, Hb, WBC, and RBC count of the codeine control group was significantly lower ($p<0.05$) than that of the remaining groups. But the RHE only group recorded the highest PCV, Hb, WBC, and RBC count. The platelets count of the codeine control group was significantly lower ($p<0.05$) when compared to negative control, RHE control and the group that received codeine alongside 1,000mg/kg RHE. The differential white blood cell counts (neutrophil, lymphocyte, eosinophil, and monocyte) of the codeine control group were significantly lower ($p<0.05$) than that of some of the remaining experimental groups, while the RHE control group recorded the highest neutrophil, lymphocyte, and eosinophil count respectively. Meanwhile, the RHE control group alongside the negative control group recorded the highest monocyte count as seen Table 1.

Discussion

The current study was conducted to examine the haematopoietic potential of rice husk methanolic extract (RHME) in codeine induced animals. Codeine in this study was considered an abused substance which is alarming in most countries in Africa.

Table 1: Hematological profile in normal, rice husk extract and codeine treated animals

Parameter	NC	COD.Only	RHE Only	COD+ 250mg RHE	COD.+ 500mg RHE	COD.+ 1,000mg RHE
PCV (%)	42.33 ± 2.08^{b}	32.33 ± 2.52^{a}	43.67± 1.53^{b}	38.67 ± 1.53^{b}	40.67 ± 3.06^{b}	41.33 ± 5.86^{b}
Hb (g/dl)	13.93 ± 0.55^{bc}	11.27 ± 0.51^{a}	14.53 ± 0.50^{c}	13.03 ± 0.64^{b}	12.93 ± 0.32^{b}	13.23 ± 1.07^{b}
RBC (x10^6/mm^3)	6.23 ± 0.40^{cd}	4.37 ± 0.31^{a}	6.47 ± 0.25^{d}	5.60 ± 0.36^{b}	5.73 ± 0.21^{bc}	5.63 ± 0.31^{b}
WBC (x10^3/mm^3)	11.97 ± 0.47^{d}	7.33 ± 1.35^{a}	14.13 ± 1.21^{e}	8.10 ± 1.28^{b}	9.87 ± 0.40^{c}	11.87 ± 0.61^{d}
Platelets (x10^3/ml)	269.67 ± 23.01^{c}	197.00 ± 19.16^{a}	271.67 ± 22.19^{c}	210.00 ± 13.00^{ab}	220.67 ± 6.03^{ab}	232.00 ± 12.77^{b}
Neutrophil (%)	29.33± 5.03^{bc}	23.33 ± 1.53^{a}	36.33 ± 1.53^{d}	28.00 ± 2.00^{ab}	30.33 ± 3.51^{bc}	34.33 ± 2.08^{cd}
Lymphocyte (%)	61.33 ± 7.57^{b}	51.00 ± 1.73^{a}	69.00 ± 1.00^{c}	56.33 ± 3.21^{ab}	58.67 ± 3.06^{b}	62.33 ± 2.52^{bc}
Eosinophil (%)	3.33 ± 1.15^{a}	2.67 ± 0.58a	5.00 ± 1.00^{b}	3.00 ± 1.00^{a}	3.33 ± 0.58^{a}	3.67 ± 0.58^{a}
Monocyte (%)	7.67 ± 0.58^{b}	5.00 ± 0.00^{a}	7.67 ± 0.58^{b}	6.00 ± 1.00^{ab}	6.00 ± 2.00^{ab}	6.67 ± 1.53^{ab}

Groups with different Superscript(s) are significantly different at p<0.05, while groups with same superscript(s) are not. Key: NC= Normal control; COD. Only = administered 10 mgkg^{-1} codeine only; RHE Only = administered 500 mgkg^{-1} rice husk extract only; COD. + 250mg RHE = administered 10 mgkg^{-1} codeine and 250 mgkg^{-1} rice husk extract; COD. + 500mg RHE = administered 10 mgkg^{-1} codeine and 500 mgkg^{-1} rice husk extract; COD. + 1,000mg RHE = administered 10 mgkg^{-1} codeine and 1,000 mgkg^{-1} rice husk extract.

The production and importation of codeine-containing syrups is under strict regulation and control by the Nigeria Government. According to Celik & Suzek (2008), some chemicals and pollutants from manufacturing waste and hazardous fumes generate free radicals and reactive oxygen species in the body, which have shown to alter haematological parameters. According to Owoade *et al*. (2019), deviation from normal haematological indices indicates the presence of toxicity or disease conditions. This study considered the effect of codeine and RHME administration on haematological indices. The assayed parameters include packed cell volume (PCV), haemoglobin (Hb), red blood cell count (RBC), white blood cell count (WBC), platelet count, neutrophil, lymphocyte, eosinophil, and monocyte. This study recorded low PCV, Hb, platelets, RBC, WBC, and its differential (lymphocyte, neutrophil, eosinophil, and monocyte) counts in codeine only treated group when compared to other groups. The observed decrease in RBCs suggest that codeine administration resulted in blood loss possibly via gastrointestinal tract bleeding, haemolysis and/or poor iron absorption in the intestine. According to Akhtar *et al.* (2021), low RBC could be linked to blood loss from gastrointestinal tract (GIT), hemolysis or poor intestinal iron absorption. According to Hamouda (2019), haemoglobin is the iron-containing oxygen-transport metalloprotein in the red blood cells of all vertebrates. Since haemoglobin is contained only in red blood cells, low RBCs would lead to low haemoglobin concentration (Sóñora *et al*., 2017) as recorded in this study. This finding is in tandem with the report by Elkhateeb *et al.* (2015), that reduced haemoglobin concentration is predominant in morphine dependent folks. The reduction in RBC, PCV and haemoglobin sugg ests that codeine misuse can manifest to anaemia. In the immune response, white blood cells and its differential are known to fight infections, guard the body against alien pathogens, and create antibodies. As per van Dixhoorn *et al*. (2016), animals with low WBC are more susceptible to disease infection, whereas those with high WBC have more disease resistance. The decrease in WBC by codeine administered rats recorded in this study is in consonant with the report of Kayode *et al*. (2021), that opium misuse supresses the immune system making the individuals more vulnerable to infective diseases. Another report by Owoade *et al.* (2019), postulated that codeine administration significantly reduced WBC, RBC and platelet count; and increased mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV) while other haematological parameters recorded no significant changes when compared with the control specimen. According to Soetan *et al*. (2013), white blood cells fight infections, defend the body against foreign organisms' invasion and produce antibodies in immune response. Thus, animals with low WBC are at high risk to diseases, while high WBC presents high resistance to diseases (Soetan *et al*., 2013). According to Moore *et al.* (2021), blood platelets are key blood clotting factor, and its low level will lead to prolonged clot-formation resulting in excessive blood loss during injury. The decreased platelet count recorded by the codeine treated group in this study shows that codeine administration could lead to thrombocytopenia. This is in line with the reports of Rasmy *et al*. (2015), that morphine administration caused a decreased platelet count. Thus, morphine administration induced thrombocytopenia. Another study by Demir & Altindag (2012) indicated that heroine caused thrombocytopenia in addicts. Four (4) weeks codeine administration also altered neutrophil, eosinophil, and monocyte count alongside lymphocyte count. Alterations in eosinophil, monocyte and neutrophil have been reported in individuals treated with codeine (Alaygut, 2014). The alterations in haematological indices recorded in this study may be attributed to increased number of free radicals generated by codeine administration. These anomalies were restored by RHE administration as recorded by the study. The haematopoietic potential of RHE could be linked to its high iron content as well as other important vitamins and minerals necessary for erythropoiesis. According to Bhadra and Deb (2020), iron is very important in maintaining many body functions, including synthesis of haemoglobin, the oxygen-carrying molecule in the blood.

Conclusion

This study revealed that high-dose codeine intake may increase the risk of blood poisoning in addition to sepsis (organ damage) which may lead to a higher risk of contracting infections. The short-term administration of high-dose codeine led to alteration of haematological profile, which was ameliorated by RHE administration. Thus, RHE is a potential haematopoietic agent. Also, considering the short-term effect, its long-term impacts could be more detrimental. Therefore, public sensitization on the potential adverse effects of codeine and other drugs of abuse should be advocated in other to significantly control drug abuse, especially among teenagers.

Recommendation

Although, the exposure period in this study was 4 weeks (sub-chronic). However, chronic period of study can be carried out organs can be assessed such as heart, lungs, brain and liver.

Declarations

Competing Interest

The authors declare no competing interest.

Authors' Contributions

Nnadiukwu, U.C. carried out the bench work and literature writing; Patrick-Iwuanyanwu, K.C., Ikewuchi, C.C. and Onyeike, E.N. oversees the supervision, review and final editing of the manuscript.

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References

Akhtar, M. F., Younas, S., Saleem, A., Baig, M. M. F. A., Sharif, A., Abdel-Daim, M. M., ... & Saleem, M. (2021). Maternotoxicity and fetotoxicity in Rattus norvegicus albinus exposed to tramadol during the late phase of pregnancy. *Birth Defects Research*, *113*(19), 1407-1421.

Alaygut, D. (2014). Codeine phosphate/paracetamol. *Reactions*, *1497*, 15–19.

Bhadra, P., & Deb, A. (2020). A review on nutritional anemia. *Indian Journal of Natural Sciences*, *10*(59), 18466-18474.

Burlando, B., & Cornara, L. (2014). Therapeutic properties of rice constituents and de- rivatives (Oryza sativa L.): A review update. Trends in Food Science & Technology, 40, 82–98.

Carney, T., Wells, J., Parry, C. D., McGuinness, P., Harris, R., & Van Hout, M. C. (2018). A comparative analysis of pharmacists' perspectives on codeine use and misuse–a three country survey. *Substance abuse treatment, prevention, and policy*, *13*(1), 1-8.

Celik, I., & Suzek, H. (2008). The hematological effects of methyl parathion in rats. *Journal of Hazardous Materials*, *153*(3), 1117–1121.

Cimo, P.L., Hammond, J.J. and Moake, J. L. (1982). Morphine-induced immune thrombocytopenia. *Archives of Internal Medicine*, *142*(4), 832–834.

Demir, B., & Altindag, A. (2012). Is There a Relationship Between Heroin Dependence and Anemia? *Addictive Disorders & Their Treatment*, *20*(4), 226-232.

Elkhateeb, A., El Khishin, I., Megahed, O., & Mazen, F. (2015). Effect of Nigella sativa Linn oil on tramadol-induced hepato-and nephrotoxicity in adult male albino rats. *Toxicology reports*, *2*, 512-519.

Fernando, S., Gunasekara, C., Law, D. W., Nasvi, M. C. M., Setunge, S., & Dissanayake, R. (2021). Life cycle assessment and cost analysis of fly ash–rice husk ash blended alkali-activated concrete. *Journal of Environmental Management*, *295*, 113140

Goufo, P., & Trindade, H. (2014). Rice antioxidants: phenolic acids, flavonoids, anthocyanins, proanthocyanidins, tocopherols, tocotrienols, γ-oryzanol, and phytic acid. *Food science & nutrition*, *2*(2), 75-104.

Hamouda, R. A., Hussein, M. H., Abo-Elmagd, R. A., & Bawazir, S. S. (2019). Synthesis and biological characterization of silver nanoparticles derived from the cyanobacterium Oscillatoria limnetica. *Scientific reports*, *9*(1), 1-17.

Jiang, H., Yan, W. H., Li, C. J., Wang, A. P., Dou, J. T., & Mu, Y. M. (2014). Elevated white blood cell count is associated with higher risk of glucose metabolism disorders in middle-aged and elderly Chinese people. *International journal of environmental research and public health*, *11*(5), 5497-5509.

Jordi, C., & Magi, F. (2003). Drug addiction. *N Engl J Med*, *349*(10), 975-986.

Kayode, A. A., Kayode, O. T., & Oridota, O. J. (2021). Alterations in the biochemical indices in Wistar rats exposed to an overdose of codeine and dextromethorphan. *Journal of Taibah University Medical Sciences*, *16*(2), 198–208.

Kim, S. J., Park, H. R., Park, E., & Lee, S. C. (2007). Cytotoxic and antitumor activity of momilactone B from rice hulls. *Journal of Agricultural and Food Chemistry*, *55*(5), 1702-1706.

Lai, M. H., Chen, Y. T., Chen, Y. Y., Chang, J. H., & Cheng, H. H. (2012). Effects of rice bran oil on the blood lipids profiles and insulin resistance in type 2 diabetes patients. *Journal of clinical biochemistry and nutrition*, *51*(1), 15-18.

Moore, C. M., & Curley, A. E. (2021). Neonatal platelet transfusions: starting again. *Transfusion Medicine Reviews*, *35*(3), 29-35.

Muthayya, S., Sugimoto, J. D., Montgomery, S., & Maberly, G. F. (2014). An overview of global rice production, supply, trade, and consumption. *Annals of the New York Academy of Sciences*, *1324*(1), 7-14.

Nenadis, N., Kyriakoudi, A., & Tsimidou, M. Z. (2013). Impact of alkaline or acid digestion to antioxidant activity, phenolic content and composition of rice hull extracts. *LWT-Food Science and Technology*, *54*(1), 207-215.

Nielsen, S., & Van Hout, M. C. (2015). Over-the-counter codeine—from therapeutic use to dependence, and the grey areas in between. In *Non-medical and illicit use of psychoactive drugs* (pp. 59-75). Springer, Cham.

Nilnumkhum, A., Punvittayagul, C., Chariyakornkul, A., & Wongpoomchai, R. (2017). Effects of hydrophilic compounds in purple rice husk on AFB1-induced mutagenesis. *Molecular & Cellular Toxicology*, *13*(2), 171-178.

O'Grady, S. (2018). Nigeria bans Codeine Cough Syrup to stop an Epidemic., addiction. But something worse could take its place. The Washington Post May 4th, 2018. *Available:https://www.washingtonpost.com /news/worldviews/wp/2018/05/04/ 28/01/2019, Assessed:*

Owoade, A. O., Adetutu, A., & Olorunnisola, O. S. (2019). Hematological and biochemical changes in blood, liver and kidney tissues under the effect of tramadol treatment. *Journal of Alcohol and Drug Depend*, *7*(327), 2.

Park, J., Gim, S. Y., Jeon, J. Y., Kim, M. J., Choi, H. K., & Lee, J. (2019). Chemical profiles and antioxidant properties of roasted rice hull extracts in bulk oil and oil-in-water emulsion. *Food chemistry*, *272*, 242-250.

Pedersen, K. M., Çolak, Y., Ellervik, C., Hasselbalch, H. C., Bojesen, S. E., & Nordestgaard, B. G. (2019). Smoking and increased white and red blood cells: a mendelian randomization approach in the copenhagen general population study. *Arteriosclerosis, thrombosis, and vascular biology*, *39*(5), 965-977.

Pode, R. (2016). Potential applications of rice husk ash waste from rice husk biomass power plant. *Renewable and Sustainable Energy Reviews*, *53*, 1468-1485.

Rasmy, A., Rahal, M., Kisana, M., Ahmad, S., & Salah, A. (2015). Morphine induced thrombocytopenia: A case report. *Journal of Case Reports and Images in Oncology*, *1*, 15-19.

Riley, L. K., & Rupert, J. (2015). Evaluation of patients with leukocytosis. *American family physician*, *92*(11), 1004-1011.

Soetan, K.O., Akinrinde, A.S., Ajibade, T. O., & . N. S. for A. P. 2013: (2013). Preliminary studies on the Guinea, haematological parameters of cockerels fed raw and processed Of, corn (Sorghum bicolor). *Proceedings of 38th Annual Conference of Nigerian Society for Animal Production*. 49–52.

Sóñora, D., Carballeira, C., Ponte, J. J., Xie, T., Luo, H., Li, S., & Mosqueira, J. (2017). Quasi-two-dimensional behavior of 112-type iron-based superconductors. *Physical Review B*, *96*(1), 014516.

Vadivel, V., & Brindha, P. (2015). Antioxidant property of solvent extract and acid/alkali hydrolysates from rice hulls. *Food Bioscience*, *11*, 85-91.

van Dixhoorn, I. D., Reimert, I., Middelkoop, J., Bolhuis, J. E., Wisselink, H. J., Groot Koerkamp, P. W., ... & Stockhofe-Zurwieden, N. (2016). Enriched housing reduces disease susceptibility to co-infection with porcine reproductive and respiratory virus (PRRSV) and Actinobacillus pleuropneumoniae (A. pleuropneumoniae) in young pigs.,. *PloS One*, *11*(9), e0161832.

Van Hout, M. C. (2014). "Doctor shopping and pharmacy hopping": practice innovations relating to codeine. *Drugs and Alcohol Today*, *14*(4), 219-234.

Wahyuni, A. S., Munawaroh, R., & Da'i, M. (2016). Antidiabetic mechanism of ethanol extract of black rice bran on diabetic rats. *National Journal of Physiology, Pharmacy and Pharmacology*, *6*(2), 106.