

Karaś Anna, Kawalko Kinga, Pondel Kamil, Bielewicz Krzysztof. Cardioprotective effects of coffee. *Journal of Education, Health and Sport*. 2022;12(10):35-40. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2022.12.10.004>
<https://apcz.umk.pl/JEHS/article/view/40030>
<https://zenodo.org/record/7094204>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences). Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przynależność dyscypliny naukowej: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

© The Authors 2022;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike.

(<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 01.09.2022. Revised: 02.09.2022. Accepted: 19.09.2022.

Cardioprotective effects of coffee

Anna Karaś, Kinga Kawalko, Kamil Pondel, Krzysztof Bielewicz

Anna Karaś annamariakaras12@gmail.com Faculty of Medicine, University of Rzeszow, Pigonia Street 6, 35-310 Rzeszow

Kinga Kawalko kingakawalko@gmail.com Faculty of Medicine, University of Rzeszow, Pigonia Street 6, 35-310 Rzeszow

Kamil Pondel pondelkml@gmail.com Faculty of Medicine, University of Rzeszow, Pigonia Street 6, 35-310 Rzeszow

Krzysztof Bielewicz krzysztofbielewicz1@wp.pl Faculty of Medicine, University of Rzeszow, Pigonia Street 6, 35-310 Rzeszow

SUMMARY

Coffee is one of the most consumed beverages among adults. Popular for its stimulant properties, it is also appreciated for its taste and is an essential part of many people's daily lives. Coffee, in addition to caffeine, contains macroelements such as sodium, potassium and magnesium, which ensure the proper functioning of the body, as well as polyphenols which are characterised by their anti-inflammatory properties. [1,2] Atrial fibrillation is the most common arrhythmia and caffeine is often considered a potential risk factor. [3] The purpose of this article is to evaluate current scientific reports on the relationship between coffee consumption and atrial fibrillation.

Keywords: coffee, caffeine, atrial fibrillation, chlorogenic acid, cardioprotection

INTRODUCTION

AND

PURPOSE

Coffee is an indispensable part of the day for many people. As a result of its stimulating properties and taste, it has gained popularity all over the world, and its consumption is systematically increasing. [1] It is served in different ways, with various additives, such as milk, sweeteners, ice cream or flavored syrups, but it retains its greatest health benefits without them. [4] Coffee, in addition to caffeine, contains macroelements such as sodium, potassium, magnesium and phosphorus and may be an overlooked source of these elements in the diet. At the same time, it is important to remember that caffeine has a diuretic effect and can lead to water and electrolyte loss. [1] Coffee contains polyphenols known for their antioxidant activity. [2]

However, most people do not think about its pro- or anti-health qualities when reaching for a cup of coffee, focusing instead on its properties such as reducing fatigue or improving cognitive function. [5]

The effects of caffeine are determined by many factors and are individually variable, depending on the dose, the foods consumed with coffee, the genetic polymorphism of enzymes involved in caffeine metabolism or personal tolerance. [6] Caffeine affects almost the entire body, modifying activity of the central nervous system, digestive system, circulatory system, urinary system and musculoskeletal system. [7] Effects on the cardiovascular system may include changes in heart rate, heart rhythm and blood pressure.

Atrial fibrillation (AF) is the most common arrhythmia worldwide, with serious and potentially fatal complications including heart failure, stroke or myocardial infarction. [8]

The following paper will provide a summary of current knowledge regarding the effects of coffee drinking on AF.

STATE OF KNOWLEDGE

Atrial fibrillation is characterized by uncoordinated electrical discharges within the electrically conductive cardiomyocytes. This leads to rapid and ineffective atrial contractions, causing the sinoatrial rhythm to be disturbed and the ventricles to contract irregularly. [8] The atrial rhythm rate can be as high as 700 per minute, which does not necessarily reflect the heart rate, which can be normal, accelerated or slowed. [9] AF can be asymptomatic or cause such symptoms as palpitations, dyspnea, chest pain, paroxysmal sweats, syncope, vertigo or anxiety [9, 10], which are adversely affected, inter alia, by increased heart rate [11].

Atrial fibrillation can be divided into:

- recognized for the first time,
- paroxysmal, usually self-limiting, lasting up to 7 days,
- persistent, occurring continuously for more than 7 days,
- persistent long-standing, lasting over 12 months, with heart rhythm control as the chosen management strategy,
- permanent, it is AF where no attempts are made to restore the sinus rhythm with the mutual consent of the patient and the physician. [12]

Risk factors for atrial fibrillation can be divided into non-modifiable, such as genetic factors [13,14] or age [15,16], and modifiable. The second group is quite extensive and can include conditions such as diabetes mellitus [17,18], hypertension [19,20], obstructive sleep apnea [21] or obesity [22,23]. Sedentary lifestyles and low physical activity may also contribute to AF [24], although some studies report that excessive exercise might provoke occurrence of AF in men [25]. Cigarette smoking, a known risk factor for many diseases, can also lead to AF. [26] It is important to note that passive exposure to cigarette smoke may also be associated with the onset of AF. [27]

A cup of coffee contains 30 to 130 mg of caffeine. [2] The half-life of caffeine in healthy people is approximately 5h. It is rapidly absorbed through the gastrointestinal tract and metabolized in the liver. The lethal dose of caffeine is about 150-200 mg/kg body weight. [5] Caffeine's influence on the cardiovascular system is based, among other things, on an increase in the catecholamines present in the blood. Its antagonistic effect on adenosine receptors indirectly leads to increased catecholamine output. Further, its inhibitory effect on phosphodiesterase may have a cardiostimulatory effect. [5, 28]

The above properties of caffeine may raise concerns about its proarrhythmic potential. However, conducted studies do not include caffeine among risk factors for atrial fibrillation. Moreover, its consumption may be expected to reduce the incidence of this arrhythmia. It has been suggested that more than two cups of coffee per day, may even reduce the risk of AF.[6,28,29] Some data suggest that the higher the consumption of coffee, exceeding 4 cups of coffee per day, the lower the risk of AF.[30]

Caffeine is a competitive antagonist of adenosine receptors, including the A2A receptor, which can be found, *inter alia*, in the heart. Increased expression of this receptor is observed in people with arrhythmias, such as atrial fibrillation. Caffeine can potentially inhibit the development of this condition by modifying the action of adenosine receptors. However, it should be remembered that caffeine's action on adenosine receptors causes an increase in serum adenosine levels. Increased levels of this nucleoside are also observed in AF patients, although it is postulated that this is due to increased expression of A2A receptors. Nevertheless, the effects of caffeine in coffee on receptors present in the heart should be further investigated. [31]

People who do not drink coffee regularly and consume it in small amounts (less than half a cup per day) have a slightly increased risk of atrial fibrillation. It is suspected that regular drinking of larger amounts of coffee, and the resulting habituation, may inhibit the effects of adenosine on the heart in the long term. Adenosine shortens the atrial refractory period, and thus caffeine's inhibition of its action may protect the heart from atrial fibrillation. [32]

Available studies indicate that the antiarrhythmic effect of coffee is not solely due to the action of caffeine, but is more attributable to other substances in it. [30] Coffee is a very rich source of polyphenols, including chlorogenic acid, which is a powerful antioxidant agent. Its content in a cup of coffee ranges from 70 to 350 mg, depending on the type of coffee and brewing method. Chlorogenic acid has an anti-inflammatory effect, reducing the formation of, *inter alia*, pro-inflammatory cytokines. [2] The above action of this polyphenol may counteract inflammatory processes that lead to atrial remodeling and associated arrhythmias, such as atrial fibrillation. [28,33]

The antioxidant and anti-inflammatory properties of polyphenols may also affect other risk factors for atrial fibrillation, such as diabetes mellitus type 2. Chlorogenic acid, contained in coffee, has a modifying effect on carbohydrate metabolism. Available literature indicates that it increases tissue insulin sensitivity, lowers fasting serum glucose levels, as well as decreases intestinal glucose absorption [2,34] and increases glucose uptake in muscle [35]. Regular coffee consumption is associated with a reduced risk of type 2 diabetes, a risk factor for atrial fibrillation. [2,34,36]

The effect of coffee consumption on blood pressure values remains a controversial topic. Several studies indicate that the increase in blood pressure values after coffee consumption is present only for a short period of time and regular coffee drinkers show tolerance to this effect, hence the risk of AF is not increased. [32,6] However, it should be remembered that caffeine contained in coffee has vasoconstrictive effects and some caution should be applied in people with known hypertension. [6]

Accelerated heart rate can exacerbate symptoms of atrial fibrillation. Coffee, by affecting the output of catecholamines, could potentially increase heart rate, although studies on this topic are inconclusive. [6] Moreover, regular coffee consumption may have a positive effect on resting heart rate by reducing it. [37]

For some time now, coffee has been appreciated for its neuroprotective properties. Ischemic stroke is one of the most serious complications of atrial fibrillation. According to several available studies, coffee protects against it and also reduces the deficits generated by ischemic brain damage. [38,39] Furthermore, moderate coffee consumption is not associated with an increased risk of AF in people with a positive medical history of arrhythmia. [40]

CONCLUSIONS

As well as its stimulating and cognitive-enhancing properties, coffee can also be part of a healthy diet. Drinking 3-4 cups of coffee a day on a regular basis does not increase the risk of atrial fibrillation, in fact, a number of available data even indicate a reduced risk of this arrhythmia in people who drink 3 or more cups of coffee a day. Consumed without additives such as sugar or milk, it retains its unique properties. As a result of its antioxidant and anti-inflammatory values, it can prevent atrial remodeling and thus the occurrence of AF. Due to its positive effect on carbohydrate metabolism, it prevents the risk factor for AF, namely diabetes mellitus type 2. Coffee also exhibits neuroprotective effects. One must be aware that coffee metabolism and the organism's response to its effects is individually variable and influenced by genetic polymorphisms.

As a rich source of polyphenols, coffee appears to be a product with beneficial qualities and its effects ought to be further investigated.

LIST OF REFERENCES:

1. Olechno E, Pušcion-Jakubik A, Socha K, Zujko ME. Coffee Brews: Are They a Source of Macroelements in Human Nutrition? *Foods*. 2021 Jun 9;10(6):1328. doi: 10.3390/foods10061328. PMID: 34207680; PMCID: PMC8227654.
2. Godos, J., Pluchinotta, F. R., Marventano, S., Buscemi, S., Li Volti, G., Galvano, F., & Grosso, G. (2014). *Coffee components and cardiovascular risk: beneficial and detrimental effects. International Journal of Food Sciences and Nutrition*, 65(8), 925–936. doi:10.3109/09637486.2014.940287
3. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res*. 2014 Apr 25;114(9):1453-68. doi: 10.1161/CIRCRESAHA.114.303211. PMID: 24763464.
4. Rashidinejad, A., Tarhan, O., Rezaei, A., Capanoglu, E., Boostani, S., Khoshnoudi-Nia, S., ... Jafari, S. M. (2021). *Addition of milk to coffee beverages; the effect on functional, nutritional, and sensorial properties. Critical Reviews in Food Science and Nutrition*, 1–21. doi:10.1080/10408398.2021.1897516
5. Institute of Medicine (US) Committee on Military Nutrition Research. Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations. Washington (DC): National Academies Press (US); 2001. 2, Pharmacology of Caffeine. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK223808/>
6. Duncan Turnbull, Joseph V. Rodricks, Gregory F. Mariano, Farah Chowdhury, Caffeine and cardiovascular health, *Regulatory Toxicology and Pharmacology*, Volume 89, 2017, Pages 165-185, ISSN 0273-2300, <https://doi.org/10.1016/j.yrtph.2017.07.025>.
7. Rodak K, Kokot I, Kratz EM. Caffeine as a Factor Influencing the Functioning of the Human Body—Friend or Foe? *Nutrients*. 2021; 13(9):3088. <https://doi.org/10.3390/nu13093088>
8. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circ Res*. 2017 Apr 28;120(9):1501-1517. doi: 10.1161/CIRCRESAHA.117.309732. PMID: 28450367; PMCID: PMC5500874.
9. Maria Trusz-Gluza, Wiktoria Leśniak, Migotanie przedsionków (AF), s.216-224, W: Interna Szczeklika, red. Gajewski P, Medycyna Praktyczna, Kraków 2019
10. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation*. 2012 Jun 12;125(23):2933-43. doi: 10.1161/CIRCULATIONAHA.111.069450. PMID: 22689930; PMCID: PMC3402179.
11. Steinberg BA, Kim S, Thomas L, Fonarow GC, Gersh BJ, Holmqvist F, Hylek E, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel JA, Chang P, Peterson ED, Piccini JP; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Increased Heart Rate Is Associated With Higher Mortality in Patients With Atrial Fibrillation (AF): Results From the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF). *J Am Heart Assoc*. 2015 Sep 14;4(9):e002031. doi: 10.1161/JAHA.115.002031. PMID: 26370445; PMCID: PMC4599492.
12. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021 Feb 1;42(5):373-498. doi: 10.1093/eurheartj/ehaa612. Erratum in: *Eur Heart J*. 2021 Feb 1;42(5):507. Erratum in: *Eur Heart J*. 2021 Feb 1;42(5):546-547. Erratum in: *Eur Heart J*. 2021 Oct 21;42(40):4194. PMID: 32860505.
13. Christophersen IE, Ellinor PT. Genetics of atrial fibrillation: from families to genomes. *J Hum Genet*. 2016 Jan;61(1):61-70. doi: 10.1038/jhg.2015.44. Epub 2015 May 21. PMID: 25994868.

14. Gudbjartsson DF, Arnar DO, Helgadóttir A, Gretarsdóttir S, Holm H, Sigurdsson A, Jonasdóttir A, Baker A, Thorleifsson G, Kristjánsson K, Pálsson A, Blondal T, Sulem P, Backman VM, Hardarson GA, Pálsdóttir E, Helgason A, Sigurjonsdóttir R, Sverrisson JT, Kostulas K, Ng MC, Baum L, So WY, Wong KS, Chan JC, Furie KL, Greenberg SM, Sale M, Kelly P, MacRae CA, Smith EE, Rosand J, Hillert J, Ma RC, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdóttir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007 Jul 19;448(7151):353-7. doi: 10.1038/nature06007. Epub 2007 Jul 1. PMID: 17603472.
15. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasán RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015; 386:154–162. doi: 10.1016/S0140-6736(14)61774-8.
16. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, MacIntyre K, McMurray JJ. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart*. 2007; 93:606–612. doi: 10.1136/hrt.2006.107573
17. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol*. 2005 Dec 7;105(3):315-8. doi: 10.1016/j.ijcard.2005.02.050. PMID: 16274775.
18. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *Am J Cardiol*. 2011; 108:56–62. doi: 10.1016/j.amjcard.2011.03.004
19. Alonso A, Krijthe BP, Aspelund T, et al.. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc*. 2013; 2:e000102. doi: 10.1161/JAHA.112.000102.
20. Verdecchia P, Angeli F, Reboldi G. Hypertension and Atrial Fibrillation: Doubts and Certainties From Basic and Clinical Studies. *Circ Res*. 2018 Jan 19;122(2):352-368. doi: 10.1161/CIRCRESAHA.117.311402. PMID: 29348255.
21. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawab R, Kirchner HL, Sahadevan J, Redline S; Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2006 Apr 15;173(8):910-6. doi: 10.1164/rccm.200509-1442OC. Epub 2006 Jan 19. PMID: 16424443; PMCID: PMC2662909.
22. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasán RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004; 292:2471–2477. doi: 10.1001/jama.292.20.2471
23. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). *Eur Heart J*. 2006 Jan;27(1):96-106. doi: 10.1093/eurheartj/ehi506. Epub 2005 Sep 23. PMID: 16183687.
24. Diouf I, Magliano DJ, Carrington MJ, Stewart S, Shaw JE. Prevalence, incidence, risk factors and treatment of atrial fibrillation in Australia: The Australian Diabetes, Obesity and Lifestyle (AusDiab) longitudinal, population cohort study. *Int J Cardiol*. 2016 Feb 15;205:127-132. doi: 10.1016/j.ijcard.2015.12.013. Epub 2015 Dec 15. PMID: 26730844.
25. Mohanty S, Mohanty P, Tamaki M, Natale V, Gianni C, Trivedi C, Gokoglan Y, DI Biase L, Natale A. Differential Association of Exercise Intensity With Risk of Atrial Fibrillation in Men and Women: Evidence from a Meta-Analysis. *J Cardiovasc Electrophysiol*. 2016 Sep;27(9):1021-9. doi: 10.1111/jce.13023. Epub 2016 Jul 7. PMID: 27245609.
26. Heeringa J, Kors JA, Hofman A, van Rooij FJ, Witteman JC. Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. *Am Heart J*. 2008 Dec;156(6):1163-9. doi: 10.1016/j.ahj.2008.08.003. Epub 2008 Oct 14. PMID: 19033014.
27. O'Neal WT, Qureshi WT, Judd SE, McClure LA, Cushman M, Howard VJ, Howard G, Soliman EZ. Environmental tobacco smoke and atrial fibrillation: the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *J Occup Environ Med*. 2015; 57:1154–1158. doi: 10.1097/JOM.0000000000000565.
28. Bodar V, Chen J, Gaziano JM, Albert C, Djoussé L. Coffee Consumption and Risk of Atrial Fibrillation in the Physicians' Health Study. *J Am Heart Assoc*. 2019 Aug 6;8(15):e011346. doi: 10.1161/JAHA.118.011346. Epub 2019 Aug 5. PMID: 31378120; PMCID: PMC6761675.

29. Cao Y, Liu X, Xue Z, Yin K, Ma J, Zhu W, Liu F, Luo J, Sun J. Association of Coffee Consumption With Atrial Fibrillation Risk: An Updated Dose-Response Meta-Analysis of Prospective Studies. *Front Cardiovasc Med.* 2022 Jul 6;9:894664. doi: 10.3389/fcvm.2022.894664. PMID: 35872898; PMCID: PMC9299433.
30. Mostofsky E, Johansen MB, Lundbye-Christensen S, Tjønneland A, Mittleman MA, Overvad K. Risk of atrial fibrillation associated with coffee intake: Findings from the Danish Diet, Cancer, and Health study. *Eur J Prev Cardiol.* 2016 Jun;23(9):922-30. doi: 10.1177/2047487315624524. Epub 2015 Dec 23. PMID: 26701875; PMCID: PMC6026854.
31. Godoy-Marín H, Duroux R, Jacobson KA, Soler C, Colino-Lage H, Jiménez-Sábado V, Montiel J, Hove-Madsen L, Ciruela F. Adenosine A2A Receptors Are Upregulated in Peripheral Blood Mononuclear Cells from Atrial Fibrillation Patients. *Int J Mol Sci.* 2021 Mar 27;22(7):3467. doi: 10.3390/ijms22073467. PMID: 33801676; PMCID: PMC8036820.
32. Xu J, Fan W, Budoff MJ, Heckbert SR, Amsterdam EA, Alonso A, Wong ND. Intermittent Nonhabitual Coffee Consumption and Risk of Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis. *J Atr Fibrillation.* 2019 Jun 30;12(1):2205. doi: 10.4022/jafib.2205. PMID: 31687073; PMCID: PMC6811341.
33. Korantzopoulos P, Letsas KP, Tse G, Fragakis N, Goudis CA, Liu T. Inflammation and atrial fibrillation: A comprehensive review. *J Arrhythm.* 2018 Jun 4;34(4):394-401. doi: 10.1002/joa3.12077. PMID: 30167010; PMCID: PMC6111477.
34. Reis CEG, Dórea JG, da Costa THM. Effects of coffee consumption on glucose metabolism: A systematic review of clinical trials. *J Tradit Complement Med.* 2018 May 3;9(3):184-191. doi: 10.1016/j.jtcme.2018.01.001. PMID: 31193893; PMCID: PMC6544578.
35. Ong KW, Hsu A, Tan BK. Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation. *Biochem Pharmacol.* 2013 May 1;85(9):1341-51. doi: 10.1016/j.bcp.2013.02.008. Epub 2013 Feb 14. PMID: 23416115.
36. Cano-Marquina A, Tarín JJ, Cano A. The impact of coffee on health. *Maturitas.* 2013 May;75(1):7-21. doi: 10.1016/j.maturitas.2013.02.002. Epub 2013 Mar 5. PMID: 23465359.
37. Nohara-Shitama Y, Adachi H, Enomoto M, Fukami A, Nakamura S, Kono S, Morikawa N, Sakaue A, Hamamura H, Toyomasu K, Fukumoto Y. Habitual coffee intake reduces all-cause mortality by decreasing heart rate. *Heart Vessels.* 2019 Nov;34(11):1823-1829. doi: 10.1007/s00380-019-01422-0. Epub 2019 May 6. PMID: 31062117.
38. Socała K, Szopa A, Serefko A, Poleszak E, Wlaź P. Neuroprotective Effects of Coffee Bioactive Compounds: A Review. *Int J Mol Sci.* 2020 Dec 24;22(1):107. doi: 10.3390/ijms22010107. PMID: 33374338; PMCID: PMC7795778.
39. Kolahdouzan M, Hamadeh MJ. The neuroprotective effects of caffeine in neurodegenerative diseases. *CNS Neurosci Ther.* 2017 Apr;23(4):272-290. doi: 10.1111/cns.12684. PMID: 28317317; PMCID: PMC6492672.
40. Glatzer KA, Myers R, Chiamvimonvat N. Recommendations regarding dietary intake and caffeine and alcohol consumption in patients with cardiac arrhythmias: what do you tell your patients to do or not to do? *Curr Treat Options Cardiovasc Med.* 2012 Oct;14(5):529-35. doi: 10.1007/s11936-012-0193-6. PMID: 22865244; PMCID: PMC3742445.