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In vivo and molecular docking studies regarded selenium nanoparticles to mitigate diabetic induction in pancreatic tissues of rats influenced by deltamethrin insecticide

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ABSTRACT

Our aim is to figure out selenium nanoparticles' (SeNPs) mitigating effect on deltamethrin induced diabetes in vivo and via molecular docking methods. Diabetic parameters were examined at both the biochemical and molecular docking levels. Four rat groups were assigned for that objective, oil fed negative control group, SeNPs orally administered group, deltamethrin orally treated group and deltamethrin associated with SeNPs administered group. Administrations lasted for one month without recovery period. The levels of glucose, cholesterol, triglycerides and anti- insulin antibodies were detected in pancreatic tissues as biochemical diabetic indicators. Molecular docking technique was conducted to visualize such influences on the molecular level via Insilco studies. Results implied elevated levels of the biochemical indicators in groups treated with deltamethrin pointing to diabetic induction while, SeNPs intervention were able to mitigate such abnormality. Molecular docking outputs were in line with the biochemical outputs pointing out to the great tendency of SeNPs to bind to the head target proteins addressed for glucose metabolism in cells and insulin reactivity thereby, competing with deltamethrin binding affinities towards such targets. In brief, in vivo and molecular docking approaches confirm the protective role that SeNPs could confer to cells in the purpose of retaining their homeostasis that ensure optimum metabolism of glucose.

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1. Introduction

Pyrethroids are those popular insecticides implicated in almost all public health issues owing to their potential pesticidal potency (Sakr and Rashed, 2023). Being classified into two types, referring to their chemical formulas and their intoxication syndromes (Ibrahim, 2016), type two pyrethroids are known to be the more effective form (Al-Amoudi, 2018).Despite of their extensive common use for insect poisoning, only few reports brought up their clinical manifestations of intoxications in humans (Prustyet al., 2015). Occupying the top rank of cellular intoxications, deltamethrin tend to cause severe cytotoxic consequences (Yadavet al., 2023). Meanwhile, prolonged exposure to deltamethrin could promptly result in severe issues which end up to glucose metabolism deteriorations (Feriani et al., 2016). Such a case was accounted by glucose turned up levels and insulin secretions regression which pancreases rely on to control glucose homeostasis (Feriani et al., 2016).Total or even partial cut down in insulin levels would result in glucose homeostasis imbalance through developing ineffective hepatic enzymes which are mainly responsible for glucose metabolism (Srinivasan, et al,. 2014).Yet, the complete picture of information regarding diabetes and pesticides interplay remains vague (Juntarawijit and Juntarawijit, 2018).

Owing to their promising medical applications, recent studies had pointed out to the therapeutic potency of SeNPs as a novel modality regarding various public health disciplines (Ahzaruddinet al., 2023).Regarding their large surface area, SeNPs showed effective protective and therapeutic properties compared to their relevant bulk materials (Ragheb et al., 2021; Parbishaet al., 2025).Many recent investigations revealed the mitigating effect of SeNPs on various diabetic issues. In 2015, Al-Quraishy et al., had confirmed the capability of SeNPs to reduce glucose levels in streptozotocin induced diabetes. Following the same track, in2016, Dkhil et al., had declared that SeNPs attenuated testicular anomalies in induced diabetic rats. In 2019;Karalis had pointed to the crucial effect of selenium in diabetes. Consisting to the same notion, in 2020, El-Borady, et al., looked for the ability of SeNPs to decrease glucose levels in model rats. Following to them were Hassan, et al., in 2021, who dedicated the role of SeNPs in getting over diabetic pancreatopathy. Then, Tarmizi et al.,(2023), submitted a collective review for the ameliorative effects of SeNPs on diabetes.

On the other hand, molecular docking is an in-silico, dry lab method that involves placing ligands and receptors at the most comfort positions in the purpose of producing stable complexes of minimal energies (Poudyal , 2021). Such complexes energies might be quantified through hydrogen bonds and electrostatic Van der waals, coulombic interactions determination (Chaudhary and Mishra, 2016).In cells, molecular docking between molecules is an issue that occurs continually and naturally (Madan et al., 2020). Grasping to the principles of molecular recognition at the molecular level is essential to ensure accurate comprehension of molecular functions and biological processes (Madan et al., 2020). Indeed, understanding the mechanical features of a biological signal is a crucial requirement that could be invested in designing novel therapeutic agents (Madan et al., 2020). Since vital biological aspects, molecular functions and even biological signals are all counted on ligand receptors interactions, the main aim of this study is to back up the mitigating effect of SeNPs on diabetes induced post deltamethrin exposure in pancreatic tissues of rats via both in vivo and molecular docking.

2. 2.0. Materials & methods

2.1. Materials

Deltamethrin powder ingredient (98%).
Serial SeNPs suspensions.

Preparation and Characterization of Nanoparticles

SeNPs suspensions were lab synthesized. Sodium selenite salt was reduced via the reducing capacity of ascorbic acid which was dropped to the salt in slow wise manner while steering at 500C till orange color was developed (Ananth et al., 2019). The prepared SeNPs are 50 nm spheres that were stabilized by dextrin polysaccharide. They were confirmed by their sharp absorption bands detected by UV-visible spectrophotometers (Beers and sizer, 1952).

Animals

Mature albino Rattus norvegicus strain weighed 180+/- 10 g and aged 9-11 weeks was used. This strain was housed in research institute of medical entomology. Animal experiments were conducted following the protocols of animal care adopted by the guidelines of national institutes of health besides the Egyptian rules for the care and use of model animals. An ethical certificate was obtained from the committee of scientific affairs of the general organization of teaching hospitals and institutes with accession number "IME 00089".

2.2. In vivo experimental Design
Experimental group design:

Four groups of rats were involved for that concern; ten rats were assigned for each group.

1. Negative control set was represented as the first group where, only corn oil was given.
2. Second rat group was administered oral doses of 27mg/kg b.w. deltamethrin twice a week, corresponding to 1/5 of its LD50 for one month

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without recovery period (WHO, 2021; IPCS 2001). This concentration was assigned to ensure effective sub lethal dose manifestations.

3. Members of the third group were orally supplied with SeNPs at dose of 0.5 mg/ kg b.w. twice a week for one month as well (Deef et al., 2019).
4. Finally, the fourth group was orally injected with deltamethrin besides SeNPs in concentrations likewise the previous steps.

All rats were scarified and their pancreases were removed. Whilst, sera were separated from blood samples which were collected from rats' aorta. Sera and pancreases were further processed for wet lab studies.

Preparation of pancreatic tissue homogenates

Pancreatic tissues were homogenized in cold media of phosphate buffer solutions, homogenates were subjected to 4000rpm centrifugation lasted for twenty minutes. The supernatants were isolated for diabetic biomarkers investigations (Ragheb et al., 2021).

Biochemical investigations

The activities of specific pancreatic biomarkers were detected to figure out the probability of diabetic onset. Levels of glucose, cholesterol, triglycerides and anti-insulin antibodies were measured in pancreatic tissue homogenates following the instruction manual of, BIOMED, Lot No: BG240418, BEACON, Lot no.: LS-4452, BIOMED, Lot No: BTG170418 and PRECHEK, EIA kit, Lot no: 119081901 respectively.

Statistical analysis

Such issues were justified by monitoring the output data of the SPSS program (SPSS Inc., USA). Such outputs were represented as standard deviations of mean values. In addition, one-way analysis of variance (ANOVA) was conducted. Discriminations through groups were assumed to be significant if $p < 0.05$. Bonferroni post hoc test was used at 95% Confidence Interval (Ragheb et al., 2021).

2.3. Molecular docking experimental design:

Forward reaction prediction

Forward reaction prediction technique was conducted to provide a screening view of the various probable reactions between deltamethrin insecticide and SeNPs (Sankaranarayanan and Jensen, 2023). All possible forward reactions were predicted and saved in standard default file, SDF file format to be available for use in reactions with default parameters.

Protein Preparation:

Protein structures were retrieved from the Uni Prot data base for 11beta-HSD1, DPP4, GLP-1 receptor, GCKR, GSK3B, PPAR-γ, and protein tyrosine phosphatase, IRS, INS1 and INS2. Such protein structures were processed through auto dock tool (Morris et al., 2009) for docking experiments.

Ligand Preparation:

The adopted compounds produced from the previous step were developed and their energy was turned down to zero via UFF force field in Avogadro 1.2.0 application program compatible with the inorganic form of such tested entities (Hanwellet al., 2012).

Binding Site Prediction:

Active binding sites of the tested proteins were defined following the steps on the CB-Dock2 server (Liu et al., 2022)

Molecular Docking:

Molecular docking step was implemented taking auto dock vina as the implementation tool. Docked conformations were subjected to primary analyses and were displayed via BIOVIA software (Eberhardt et al., 2021).

3. Results

3.1. Selenium nanoparticles characterization

SeNPs preparation was confirmed by examining the particles' absorption bands detected by UV-Vis spectrophotometer at wave lengths ranged from 200nm to 300 nm according to Ananth et al., 2019 (Figure1).

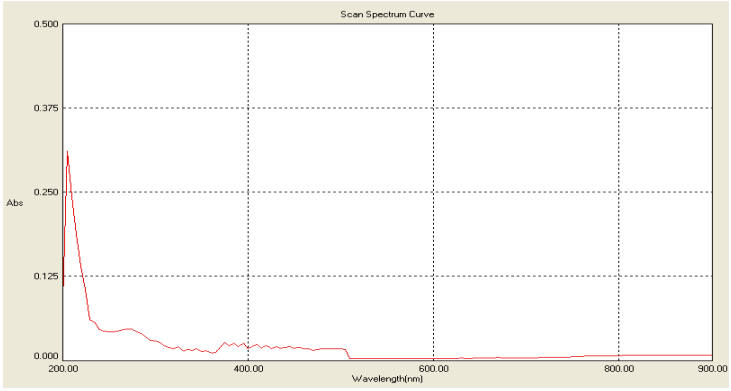

Figure 1: Distinctive absorption band of selenium nanoparticles displayed by UV-visible spectrophotometer.

3.2. Average weights:

Upon studying the subjects mean weights, results pointed out to reduction in the mean body weights of rats treated with deltamethrin. However, such weight losses were restored in rats treated with SeNPs (Table 1).

Table (1): Average total body weights

Groups	Average total body weight (g) ± SE
Control	225±1.34
0.5 SeNPs mg/Kg	228±2.23**
27 deltamethrin mg/kg	228±2.23**
27 deltamethrin mg/kg and 0.5 SeNPs mg/Kg	217±1.34**

Data are displayed as average ± SE, ** is highly significant= P< 0.001, * is significant = P<0.005, NS is non-significant= P>0.005, n=10.

3.3. Glucose, cholesterol and triglycerides estimations

Glucose, cholesterol and triglycerides levels were dramatically increased in deltamethrin administered rats (Table 2) however, selenium nanoparticles intervention significantly reduced the levels of such markers.

3.4. Average Anti- insulin Ab levels in pancreatic tissues:

Investigating the average levels of insulin antibodies in pancreatic tissue homogenates was crucial; results implied marked increase of such marker in deltamethrin administered rats. Fortunately, SNPs treated rats showed relative decreased values (Table 3)

3.5. Docking results

This study investigated the potential anti-diabetic properties of SeNPs and SeNPs- deltamethrin reaction products through molecular docking methods. In order to proceed through docking insights, Insilco prediction reaction was conducted between the tested parameters namely, SeNPs and deltamethrin to predict the product which would be tested for docking among several receptors (Figure 2).

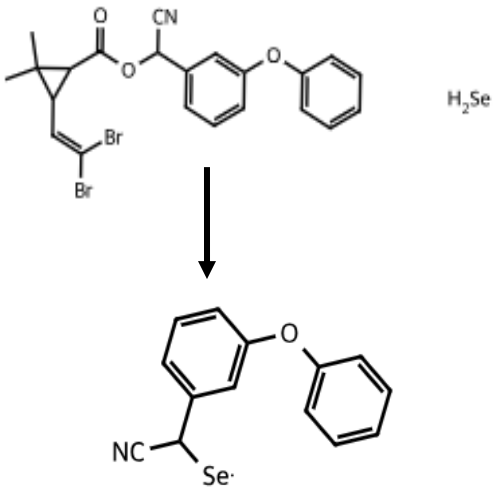

Figure (2): reaction prediction for SeNPs and deltamethrin

Upon docking, deltamethrin's strong binding to multiple cellular targets suggests that it could interfere with normal insulin signaling and consequently could affect cellular glucose metabolism. This could potentially elaborate its toxic effects on insulin resistance as shown in Table (4).

Deltamethrin, SeNPs and Deltamethrin-SeNPs were evaluated for their binding affinities to several cellular protein targets associated with diabetes, including 11beta-HSD1, DPP4, GLP-1 receptor, GCKR, GSK3B, PPAR-γ, and protein tyrosine phosphatase, IRS, INS1 and INS2. Molecular docking results revealed limited binding affinities for SeNPs among all the targets with binding energies ranged between -0.5 and -1.3 kcal/mol. In contrast, deltamethrin exhibited stronger binding affinities, particularly for PPAR-γ (-9.7 kcal/mol), 11beta-HSD1 (-9.1 kcal/mol), and GCKR (-8.3 kcal/mol). However, it showed positive binding energy for DPP4 (2.8 kcal/mol), suggesting unfavorable binding. The reaction product of SeNPs and deltamethrin demonstrated moderate binding affinities within all subjects ranged between -5.1 and -7.4 kcal/mol with the strongest affinity for PPAR-γ. The reaction product between SeNPs and deltamethrin shows limited binding affinities compared to deltamethrin alone as implied in Figures 3(a, b & c), 4 (a, b & c).

4. Discussion

For more than a decade, different elaborations were submitted to elucidate the root cause of hyperglycemic manifestations post deltamethrin exposure. Scientists attributed such manifestations to the observed increase of glucose in blood, nor adrenaline beside adren¬aline indexes in plasma of rats exposed to oral del¬tamethrin administrations (Cremer and Seville, 1982) suggesting that elevated adrenalin levels is one cause that lead to glucose levels turn up(Bradbury et al., 1982). Others referred the condition to the phys¬iological reactions which were developed as a result of pyrethroids actions on the supra-spinal centers (Bradbury et al., 1982). Recently, the situation towards such hyperglycemic induction was attributed to that imbalance in the secreted insulin from the pancreatic islets (Kim et al., 2015). This imbalance is a consequent result of the exerted stress on the sensitive voltage calcium channels which in turn leads to hyperglycemic induction (Kim et al., 2015).However and whatever were the causes, eventually it was revealed that deltamethrin exposure induce hyperglycemic effect or diabetes. Initially, diabetes is a chronic pancreatic disease

manifested as a metabolic disorder where pancreases become unable to secret adequate insulin amounts which consequently causes elevated blood glucose levels (Hassan et al., 2023). Such elevated glucose levels, cause severe complications which might be life threatening (Alipin et al., 2017).

Since the past decade, selenium was known to act as an antioxidant which is capable of protecting the islets of pancreas from the oxidative stress and retain their healthy state (Karalis, 2019). In contrast to sele¬nite, SeNPs came to be more biocompatible, with higher permeability, better antioxidant capability, smooth and safe in intestinal absorption and exhibit higher affinity properties (Deng et al., 2019).Hence, this study aimed at looking into the protective potency that SeNPs could confer to deltamethrin induced diabetic rats regarding in vivo and in silicoconcerns.

Concerning the chemical characterization of SeNPs which were involved in this study, their UV-visible absorption spectrum was displayed at wave lengths ranging between 200nm and 300nm, this finding was in accordance with that described by Ananth et al., (2019). Upon examining total body weights, SeNPs could restore body weights of rat subjects in comparison to those who were only deltamethrin administered. Changes in body weight can give several indications to come across any unexpected changes in metabolic mechanisms. Moreover, observing differences in body weights confers a vivid picture on the ability of SeNPs to get over weight loss in diabetic mice. Such findings were in accordance with reports implied in several researches(Dekhilet al.,2016 ;Tarmizi et al., 2023;Karas et al., 2024).Elevation in glucose levels is the key indicator of diabetes. In this study results pointed to a decrease of glucose levels in rats influenced with SeNPs when referred to those who orally injected with deltamethrin only. Acting as a protective and anti- diabetic agent, average glucose levels were observed to decrease in rats which were treated with deltamethrin associated with SeNPs. Such findings were also in accordance with many recent studies (Dekhilet al., 2016; Bishtet al., 2022; Tarmiziet al., 2023; Karaset al., 2024). A recent report has walked through the role of SeNPs not only in mitigating the levels of glucose but also, in elevating insulin production (El-Boradyet al. 2020). In accordance to the results of this study, Zeng et al. (2018) have also reported a significant turn down of glucose levels which were SeNPs dose dependent. In recent scientific reports, it was a matter of research to account for the way selenium could reduce glucose levels and lead to hypoglycemic effect. Starting with its popular antioxidant potency, selenium is capable of conferring better diabetic manifestations via doing away with lipoprotein oxidations and their consequent oxidative stresses. Further, selenium could add up to blood glucose levels enhancing insulin signaling, pyruvate metabolism and glycolysis (Ojeda et al., 2023; Hassan et al.2021). Finally, we should not forget the similarity of functions between selenium and insulin that could make balance in enzymes activities essential for both glycoly¬sis and gluconeogenesis and in facilitating glucose transport to the cells as well (Hawang et al., 2007).

Indeed, investigating lipid metabolic markers was mandatory; since diabetes is the true fellow of dyslipid-emia where abnormal lipid profile is always the main alarm (Nelson et al., 2018). Expecting turned up cholesterol and tri¬glyceride levels in diabetic cases and confirming such anticipates could bear out the supporting role of SeNPs in regulating elevated lipids (Karas et al., 2024). Consistent to the current study results, a decrease in cholesterol and triglycerides levels in rats treated with SeNPs was confirmed in contrast to those who were vulnerable to deltamethrin only. Deltamethrin exposure could lead to such metabolic abnormalities either via insulin turned down production or insulin resistance which in both cases could lead to fatty acids sudden entrance to the liver which influence the vital processes of lipid metabolism in turn (Abdel Maksoud et al., 2020). Returning to the protective role of SeNPs towards such metabolic issues, they are characterized by exhibiting large surface area which gives them the potency for adsorbing, fixing and serving as carriers to vital cellular requirements (Karas et al., 2024). Such unique attitude of SeNPs renders them an appropriate choices for effective treatment strategies (Ragheb et al., 2021 ;Tarmiziet al., 2023; Karas et al., 2024). What makes SeNPs had this ability to catch up cholesterol and triglycerides levels to their normal ranges (Tarmizi et al., 2023; Abdel Maksoud et al. 2020; Abdulmalek and Balbaa 2019; Khater et al. 2021; Zeng et al. 2018), is attributed to their flavonoid rich content which suppresses the action of cAMP dependent protein phosphokinases that affect the phosphorylation processes in the cholesterol biosynthesis (Mohamed et al., 2021). In other words; SeNPs work on hyperlipidemia by supporting the metabolism of hepatic cholesterol besides gradual removing to tissue damages developed out of oxidative stresses (Wan et al. 2021).

Since it was discovered in 1920s, diabetes had been effectively controlled with insulin (Sims et al., 2021). Since then, immunological reactions to insulin have become increasingly common (Chen et al., 2023). Antibodies directed against insulin were observed in some clinical cases as it was manifested by the first type of

diabetes or in the autoimmune insulin syndrome or finally, it may be associated as a secondary manifestation upon treatment with exogenous insulin (Chen et al., 2023).The ultimate relation between insulin antibodies and diabetic treatments depend mainly on complete monitoring of insulin antibodies without focusing on any specific insulin antibodies subclasses(Chen et al., 2023).Worthy to mention is that pesticides are known to be lethal to the immune cells. The attained scenarios when deltamethrin invade the immune system are restricted to four pathways (Kumar et al., 2015). The first and the best of which is that deltamethrin would not exert its toxic effect on the immune system. The following probable manifestation is an immune response enhancement which definitely would end up to autoimmune diseases. The third anticipated effect of deltamethrin invasion is immune response turn down effect which is known as immune suppression effect. Finally, deltamethrin invasion would augment the progress of hypersensitivity reactions (Kumar et al., 2015). In this study levels of insulin antibodies were measured to stand on the cellular details that may help to elucidate the beneficiary role of SeNPs towards diabetes. As such, this study highlighted turned down levels in insulin antibodies levels of rats which were treated with SeNPs upon comparing to rats in the negative control groups. However, such antibodies levels were elevated in tissues of rats where deltamethrin was administered. Such findings might be explained in the basis of deltamethrin potency to induce diabetes via exerting its toxic effect on the beta pancreatic cells manifested as elevated glucose in deltamethrin treated subjects, meanwhile it causes immune response progression which ends up to autoimmune diseases manifested in the increased average levels of insulin antibodies (Chen et al., 2023).As it was described by Han et al.,(2023) in justifying such syndrome concerned with insulin autoimmune manifestations, the state where self-antibodies tend to bind to insulin or to pro-insulin which consequently lead to an early postprandial hyperglycemia (Lin et al., 2023).

In this study, insulin antibodies were developed in rats treated with deltamethrin as a consequent of deltamethrin induced immune diseases and the beneficiary role of SeNPs was observed to decrease the levels of such antibodies as it controlled the levels of glucose as well.

By means of reason, one may comprehend some facts that were established by multidisciplinary scientific branches about the beneficiary role of SeNPs to protect viable cells from toxic agents. However, it is not possible for reason on its own to find out and learn about all the details of this branch of knowledge unless a vivid picture or at least a tangible picture is to be imagined. Conferring tangible picture for the reactions that took place between SeNPs and deltamethrin would help in a great manner to assume the mechanism through which SeNPs exert its action in cell protection. Insilico studies did that in the best manner striving in that noble cause (Madanet al., 2020). In this study, upon docking deltamethrin to multiple cell targets the obtained strong bindings suggest the capability of deltamethrin to interfere with normal insulin signaling and glucose metabolism which could potentially explain its toxic effects on insulin resistance and the consequent hyperglycemic effect as shown in the revealed results. Such interactions between deltamethrin and different cell metabolic ligands which were conducted via molecular docking would greatly help in predicting the type of signals produced (Arya and Kaur, 2022) and the consequence of such binding. However, the weak binding affinities of the reaction product of both SeNPs and deltamethrin compared to deltamethrin alone for the proteins 11beta-HSD1, GCKR, PPAR-γ, INS1, pTyr INS2,GLP1and IRS, which are significant cell targets is particularly noteworthy as these proteins play important roles in glucose metabolism and insulin sensitivity(Gaba, et al., 2010). These attenuated binding affinities suggest that SeNPs might mitigate the deltamethrin's effects by forming a compound that interacts less strongly with these key proteins. Such weak binding affinity to the reaction product could explain the observed reduction in insulin antibody levels in the wet lab experiments upon SeNPs intervention, suggesting the protective role of SeNPs towards these target proteins hence, controlling diabetes and insulin sensitivity as well. In other words; by reducing deltamethrin's interaction with cell key proteins, SeNPs might prevent the disruption of normal insulin signaling, thereby reducing the immune response against insulin (Madanet al., 2020). In general, docking results confirmed and conferred an elucidation for the protective potency that SeNPs could provide to encounter deltamethrin’s adverse effects on insulin resistance by modifying deltamethrin's ability to interact with key proteins in the insulin signaling pathway (Al-Tameemi, 2022).

In spite of being promising, such results are in need to address several limitations in future concerns. Experimental validation through in vitro, in vivo and in silico studies is required to back up the predicted anti-diabetic effects and safety profiles of SeNPs. The effective concentrations for SeNPs anti-diabetic activity versus potential toxicity should be also determined to establish dose-response relationships.

Conclusion

In conclusion, the biological in vivo and the computational in silico studies suggest that SeNPs exhibit potential anti-diabetic potency which act through multiple mechanisms. In vivo, SeNPs show promising role in controlling the levels of glucose, cholesterol, triglycerides and insulin anti bodies. And in silico, SeNPs show promising binding affinities to cell key targets involved in glucose homeostasis and insulin sensitivity. However, extensive further researches are required to validate such findings and assess SeNPs safety and efficacy in biological systems before considering them for therapeutic development. The intervention of molecular docking confirmation tool provides a valuable confirming point for the identification and optimization of novel anti-diabetic compounds hence, paving the way for more targeted experimental studies in the future.

Ethics approval

Not applicable.

Availability of data and material

Not applicable.

Conflict of interest

The authors declared no potential conflicts of interest concerning this article's research, authorship, and publication.

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References

[1] K. AL-Jammali, Prediction of heart diseases using data mining algorithms, Informatica, **47**(5), 57-62 (2023).

[2] H.B.F. David and S.A. Belcy, Heart disease prediction using data mining techniques, International Journal of Scientific & Engineering Research, **9**(1), 1817-1823 (2018).

[3] A. Janosi, W. Steinbrunn, M. Pfisterer, and R. Detrano, Heart disease [Dataset]. UCI Machine Learning Repository. https://doi.org/10.24432/C52P4X (1989).

[4] K. Govindaraju and G. Kalimuthu, Heart disease analysis and prediction with machine learning techniques using cleveland dataset, In International Symposium on Intelligent Computing Systems (pp. 20-43). Cham: Springer Nature Switzerland (2024)

[5] J.D. Kelleher, M. Mac-Carthy, and O. Korvir, Fundamentals of machine learning for predictive data analytics: Algorithms, worked examples, and case studies. MIT Press (2015).

[6] R.S. Sutton and A.G. Barto, Reinforcement learning: An introduction (2nd ed.). MIT Press (2018).

[7] J. Brownlee, Machine learning mastery with Python: Understand your data, create accurate models, and work projects end-to-end. Machine Learning Mastery, Jason Brownlee, San Francisco (2016).

[8] F.Y. Osisanwo, J.E.T. Akinsola, O. Awodele, J.O. Hinmikaiye, O. Olakanmi, and J. Akinjobi, Supervised machine learning algorithms: Classification and comparison, International Journal of Computer Trends and Technology (IJCTT), **48**(3), 128–138 (2017).

[9] D. Shah, S. Patel, and S.K. Bharti, Heart disease prediction using machine learning techniques, SN Computer Science, **1**(6), 345 (2020).

[10] M. Fatima and M. Pasha, Survey of machine learning algorithms for disease diagnostic, Journal of Intelligent Learning Systems and Applications, **9**(01), 1-16 (2017).

[11] K. Pahwa and R. Kumar, Prediction of heart disease using hybrid technique for selecting features, In: 2017 4th IEEE Uttar Pradesh section international conference on electrical, computer, and electronics (UPCON). IEEE, 500–504 (2017).

[12] S. Pouriyeh, S. Vahid, G. Sannino, G. De Pietro, H. Arabnia, and J. Gutierrez, A comprehensive investigation and comparison of machine learning techniques in the domain of heart disease, In: 2017 IEEE symposium (2017).

[13] T. Liu, A. Krentz, L. Lu, and V. Curcin, Machine learning based prediction models for cardiovascular disease risk using electronic health records data: systematic review and meta-analysis, European Heart Journal-Digital Health, **6**(1), 7-22 (2025).

[14] R. Chauhan, P. Bajaj, K. Choudhary, Y. Gigras, Framework to predict health diseases using attribute selection mechanism, In: 2015 2nd international conference on computing for sustainable global development (INDIACom). IEEE, p. 1880–84 (2015).

[15] H. Bouali, J. Akaichi, Comparative study of different classification techniques: heart disease use case, In: 2014 13th international conference on machine learning and applications. IEEE, p. 482–86 (2014).

[16] S. Xu, Z. Zhang, D. Wang, J. Hu, X. Duan, and T. Zhu, Cardiovascular risk prediction method based on CFS subset evaluation and random forest classification framework. In: 2017 IEEE 2nd international conference on big data analysis (ICBDA), IEEE, p. 228–32 (2017).

[17] D.W. Hosmer, S. Lemeshow, and R.X. Sturdivant, Applied Logistic Regression (3rd ed.). Wiley (2013).

[18] C. Cortes and V. Vapnik, Support-vector networks, Machine Learning, **20**(3), 273–297 (1995).

[19] J.H. Friedman, Greedy function approximation: A gradient boosting machine. The Annals of Statistics, **29**(5), 1189–1232 (2001).

[20] D.E. Rumelhart, G.E. Hinton, and R.J. Williams, Learning representations by back-propagating errors, Nature, **323**(6088), 533–536 (1986).

[21] T. Chen and C. Guestrin, XGBoost: A scalable tree boosting system, Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, 785–794 (2016).

[22] M. Niazkar, A. Menapace, B. Brentan, R. Piraei, D. Jimenez, P. Dhawan, and M. Righetti, Applications of XGBoost in water resources engineering: A systematic literature review (Dec 2018–May 2023). Environmental Modelling & Software, **174**, 105971 (2023).

[23] G. Ke, Q. Meng, T. Finley, T. Wang, W. Chen, W. Ma, Q. Ye, and T. Liu, LightGBM: A highly efficient gradient boosting decision tree, Conference Advances in Neural Information Processing Systems, 30 (2017).

[24] D.N. Wang, L. Li, and D. Zhao, Corporate finance risk prediction based on LightGBM. Information Sciences, **602**, 259-268 (2022).