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RESEARCH ARTICLE OPEN ACCESS

A REVIEW OF POLOXAMER 407 INDUCES HYPERLIPIDEMIA IN VIVO STUDIES

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ABSTRACT

Poloxamer-407, a surfactant and emulsifier commonly used in pharmaceutical formulations, has attracted attention as a potential contributor to increased lipid levels in the body based on in vivo research. A systematic review was conducted in January 2023 to examine the mechanisms by which poloxamer 407 contributes to the development of hyperlipidemia in in vivo studies published between 2010 and 2022, yielding 1240 results. Study selection was done using the PRISMA method. Manual screening, quality assessment, and data extraction from the search results were rigorously conducted in accordance with inclusion and exclusion criteria. Seventeen identified studies showed a correlation between the use of poloxamer 407 and a significant increase in blood lipid levels, creating conditions of hyperlipidemia. The significance of these findings lies in a deeper understanding of the potential side effects of poloxamer 407, especially in the context of human health. Its implications can guide further developments in the use of this compound or similar chemicals in pharmaceutical formulations. Therefore, this research provides a foundation for further studies that can detail the long-term impacts, underlying mechanisms, and possible mitigation strategies to manage side effects associated with the use of poloxamer 407.

I. INTRODUCTION

Poloxamer 407 is a nonionic surfactant, commonly used in pharmaceutical formulations and biomedical research due to its unique properties. It is a triblock copolymer composed of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO), which imparts its amphiphilic nature and self-assembling behavior [1-3]. Poloxamer 407 has been extensively studied for its applications in drug delivery systems, tissue engineering, and as a solubilizer and stabilizer in pharmaceutical formulations [4].

However, recent studies have raised concerns regarding the potential adverse effects of Poloxamer 407 on lipid metabolism and its role in inducing hyperlipidemia in vivo. Hyperlipidemia is a condition characterized by elevated levels of lipids, such as cholesterol and triglycerides, in the bloodstream. It is a major risk factor for cardiovascular diseases, including atherosclerosis and coronary artery disease [5].

Studies investigating the effects of Poloxamer 407 on lipid metabolism have demonstrated its ability to disrupt the balance of lipids in the body. In animal models, administration of Poloxamer 407 has been shown to increase serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, while reducing high-density lipoprotein (HDL) cholesterol levels [6]. These changes in lipid profile closely resemble the dyslipidemic pattern observed in hyperlipidemia [7].

One proposed mechanism for the hyperlipidemic effects of Poloxamer 407 involves its disruption of the integrity of cell membranes, particularly in hepatocytes [8]. This disruption can lead to increased release of lipids into the bloodstream, contributing to elevated lipid levels [9]. Additionally, Poloxamer 407 has been shown to inhibit the activity of lipoprotein lipase, an enzyme responsible for the breakdown of triglyceride-rich lipoproteins [10].

The implications of Poloxamer 407-induced hyperlipidemia are significant, especially considering its widespread use in

pharmaceutical formulations and biomedical research. It highlights the need for caution when utilizing Poloxamer 407 in drug delivery systems and emphasizes the importance of assessing its potential effects on lipid metabolism [11].

This review aims to provide a comprehensive evaluation of the current literature on the relationship between Poloxamer 407 and hyperlipidemia in in vivo studies. By examining the available evidence, this review will contribute to a better understanding of the potential risks associated with the use of Poloxamer 407 and help guide future research and development efforts in the field.

II. METHODS

The systematic review methodology aims to identify and summarize research articles related to the use of Poloxamer-407 in treating metabolic syndrome. The systematic review is conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method [12] to ensure the process is transparent and reported accurately.

II.1 DATA SOURCES

Literature search was conducted using the keywords: Poloxamer-407, in vivo, rats, and hyperlipidemia. International databases were sourced from references or literature published on PubMed, NCBI, MDPI, Web of Science, and Springer, using connectors such as "and" or "or."

II.2 STUDY SELECTION

The study selection was conducted using the PRISMA flow diagram (Figure. 1). Search results were evaluated sequentially based on titles and abstracts. Inclusion criteria included: 1) publications in English, 2) literature published from 2010 to 2022, 3) literature related to hyperlipidemia, 4) involving only Poloxamer-407. Excluded literature comprised publications before 2010, non-English publications, literature unrelated to hyperlipidemia, and other Poloxamer variants. Selected literature was filtered for duplicates.

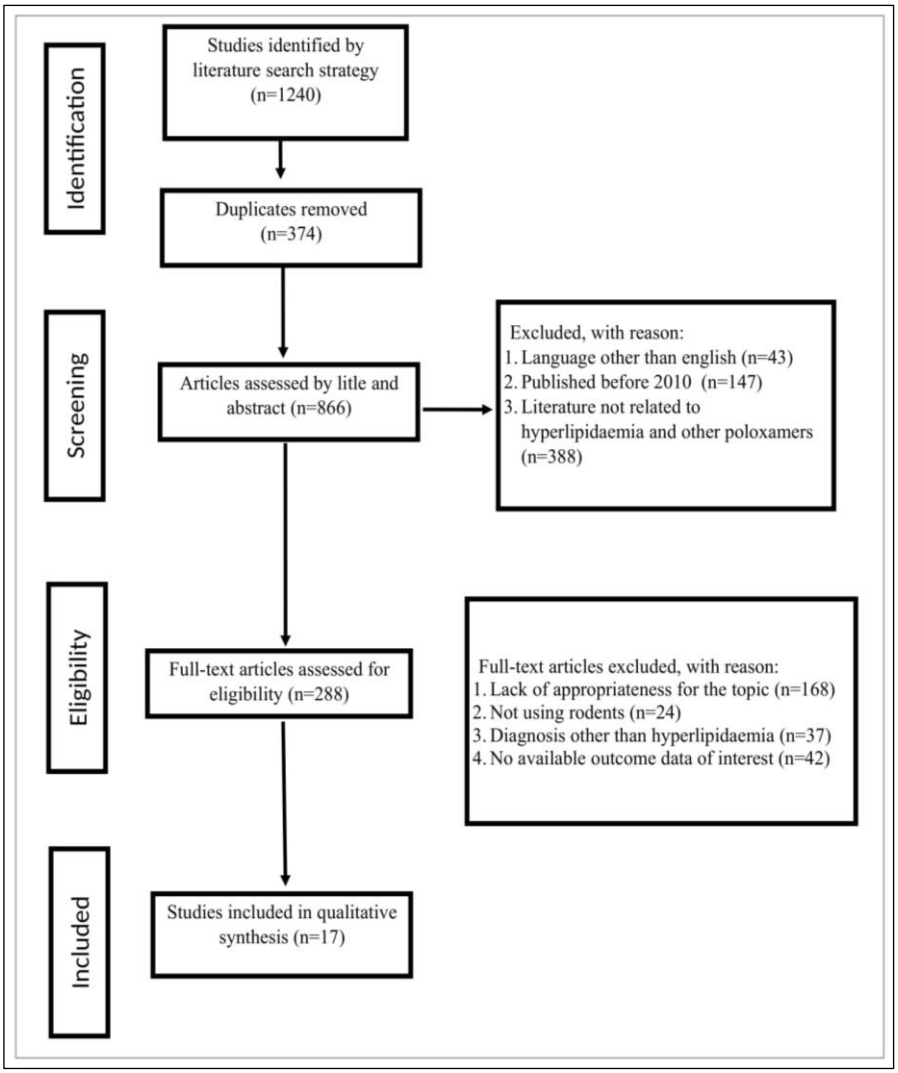

Figure 1: Flow chart for article selection.
Source: Authors, (2024)

II.3 DATA EXTRACTION

He matrix method was then employed to aid in summarizing and critiquing the selected studies. This matrix includes author (year), country, subject, dosage and method, key findings, as presented in Table 1. Data analysis was conducted by amalgamating relevant source references and adequate literature, facilitating data collection by providing sufficient understanding and explanation

III. RESULTS AND DISCUSSION

III.1 RESULT

Poloxamer copolymer, sometimes known as Poloxamer 407, is a hydrophilic non-ionic surfactant commonly used in

various pharmaceutical and cosmetic formulations. Poloxamer 407 is a triblock copolymer consisting of two hydrophilic polyethylene glycol groups flanking a hydrophobic polypropylene glycol main group [13].

However, some studies have revealed that P407 can cause adverse side effects, including hyperlipidemia [14]. In this review, we will discuss and analyze findings from in vivo studies evaluating the relationship between P407 and the development of hyperlipidemia in experimental animals.

Animal-based studies on hyperlipidemia with the administration of Poloxamer-407 (P407) are presented in the table 1.

Table 1: Characteristics and key findings of selected articles (n=17).

AUTHOR, (YEAR)	COUNTRY	SUBJECT	DOSAGE AND METHOD	KEY FINDINGS
Hetal et al, 2013 [15]	Canada	Male Sprague Dawley rats	Single IP of 0.5 and 1g/kg	↑TC, ↑TG, ↑LDL, ↓HDL, and ↑leptin, ↓adiponektin
Thomas et al, 2012 [16]	Kansas City	Male Sprague Dawley rats	Single IP of 0.3 g/kg	↑TC and ↑HMG-CoA reductase activity
Yeom et al, 2018 [17]	Republic of Korea	Male Sprague Dawley rats	Single IP of 0.4 g/kg	↑TC, ↑TG, ↓HDL, and ↑LDL
Ruchel et al, 2016 [18]	Brazil	Male Wistar Rats	Single IP of 0.5 g/kg	↑TC, ↑TG, ↓HDL, and↑ LDL
Korolenko et al, 2013 [19]	Russia	Male CBA mice	IP of 0.5 g/kg twice per week for 1 month	↑TC, ↑TG, ↓HDL, and ↑LDL
Susana et al, 2017 [20]	Spain	Male Golden Syrian Hamsters	Periodically IP of 50 mg/kg every 72 h until 4 and 30 days	↑Lyso-PLs, ↓NEFAs, ↑TC, ↓HDL, ↑LDL, ↓LCAT, ↓sPLA2-IIA, ↑PON1
Leon et al, 2016 [21]	Canada	Male mice	IP of 0.5 g/kg	ACAT2 protein expression were not altered by P-407, ↑ LDL, ↑CL, ↑TG, ↑HMG-CoA reductase activity
Kumar et al, 2021 [22]	India	Male Wistar rats	Single IP of 0.5 g/kg	↑HOMA-IR index, ↑TG, ↑CL, ↓FRAP, ↓GSH, ↑PMRS, ↑AGE, ↑MDA, ↑PCO, ↑AOPP, ↓PON-1, ↑TNF-α and ↑IL-6, ↑SGPT and ↑SGOT
Jardan et al, 2021 [23]	Saudi Arabia	Male Wistar rats	Single IP of 1 g/kg	↑CYP3A, ↑TG, ↑CL, ↑LDL
Manzoni et al, 2020 [24]	Brazil	Male Wistar rats	Single IP of 0.5 g/kg	↑MDA, ↓SOD, ↓GST, ↓CAT, ↑ALT, ↑AST, ↑LDL, ↓HDL,
Zanwar et al, 2014 [25]	India	Male Wistar rats	Single IP of 0.5 g/kg	↑TC, ↑TG, ↓HDL, ↑VLDL
Yeom et al, 2018 [17]	Republic of Korea	Male Sprague Dawley rats	Single IP of 0.4 g/kg	↑TC, ↑TG, ↑ LDL, ↓HDL, ↑SREBP-2, ↑HMG-CoA reductase activity
Omari et al, 2016 [26]	Republic of China	Male Sprague Dawley rats	Single IP of 0.5 g/kg	↑TC, ↑TG, ↑ LDL, ↓HDL, ↓SOD, ↓GSH-PX, ↑MDA, ↑ALT, ↑AST
Ruchel et al, 2017 [18]	Brazil	Male Wistar rats	Single IP of 0.5 g/kg	↑TC, ↓HDL, ↑ LDL, ↑AST, ↑ALP, ↑ALT
Park et al, 2016 [27]	Republic of Korea	Male C57BL/6NTacSam mice	Single IP of 0.5 g/kg	↑TC, ↑TG, ↑ LDL, ↓HDL, ↑FAS, ↑ACC, ↑SREBP-2, ↑HMCR, ↑LDL, GAPDH, ↑SREBP-1c
Zuberu et al, 2017 [28]	Nigeria	Male Wistar rats	Single IP of 0.5 g/kg	↑TC, ↓HDL, ↑LDL, ↑AST, ↑ALP, ↑ALT
Manzoni et al, 2020 [29]	Brazil	Male Wistar rats	Single IP of 0.5 g/kg	↑TC, ↓HDL, ↑LDL, ↑AST, ↑ALP, ↑ALT, ↓SOD, ↓CAT, ↓GST

Source: Authors, (2024).

III.2 DISCUSSIONS

The Effect of Poloxamer-407 on Lipid Profile

Several in vivo studies have been conducted to evaluate the influence of P407 on lipid profiles in experimental animals. For instance, research conducted by Korolenko et al. (2013), using rats as an animal model, indicates that intravenous administration of P407 can elevate the levels of total cholesterol and triglycerides in the rats' blood [19]. Similar results were also reported by Naik et al. (2013), who found that oral administration of P407 to rabbits led to a significant increase in low-density lipoprotein (LDL) concentrations and plasma triglycerides [30].

The Mechanism of Inducing Hyperlipidemia by Poloxamer-407

The mechanism of hyperlipidemia has been investigated in numerous in vitro and in vivo experiments [31]. Currently, it is

possible to induce hyperlipidemia in test animals in various ways. Hyperlipidemia can be triggered by certain chemicals, but only when consumed over an extended period and gradually over time [32]. One such substance is Poloxamer 407 (Pluronic®-M 127, P-407), which has been shown to significantly increase plasma triglyceride and cholesterol levels in several animal species, including rats [33], [34], mice [35-37], and rabbits [38]. Studies by Wasan et al. (2003) suggest that P407 can disrupt lipid metabolism by inhibiting the activity of lipoprotein lipase (LPL), which plays a role in breaking down lipoproteins and transporting triglycerides [39]. Another study by Leon et al. (2006) indicates that P407 can affect the expression of genes involved in lipid metabolism, including increased expression of genes regulating cholesterol synthesis in the liver [40]. One of the most intriguing hyperlipidemia models is P407, with a mechanism marked by increased TG levels due to: (1) inhibition of lipoprotein lipase; (2) increased TC levels due to indirect stimulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase) activity, a rate-limiting enzyme in TC biosynthesis; and (3) reduced LDL receptor expression in all cholesterol-producing cells [41]. The P407 animal model can be influenced by the choice of: (1) various rodent species [20], [38], [41-43], (2) dose concentrations ranging from 300 mg/kg to 1500 mg/kg body weight [44], with the latter dose being preferred for mild hyperlipidemia; and (3) depending on the desired outcomes [45], either single treatment or chronic treatment [8], [20], [44], [46] via intraperitoneal (IP) injection.

Comparison with Other Studies

In addition to the studies mentioned above, several other studies have also reported the hyperlipidemic effects of P407 in experimental animals. For instance, Johnston et al. (2004) conducted a similar study using a rat model and found that P407 could also increase the levels of free fatty acids in the blood, which is a significant risk factor in the development of hyperlipidemia [47]. This finding aligns with the research by Johnson et al. (2010), indicating that P407 can influence the activity of adipose lipase enzymes, responsible for breaking down fats in adipose tissue [48].

IV. CONCLUSIONS

The findings from the discussed in vivo studies indicate that P407 has the potential to induce hyperlipidemia in experimental animals. The clinical implications of these findings need to be seriously considered, especially in the context of P407's use in pharmaceutical and cosmetic formulations. Furthermore, further research is required to understand the underlying mechanisms of the hyperlipidemic effects of P407 and to evaluate its potential risks in humans.

V. AUTHOR'S CONTRIBUTION

Conceptualization: Neti Eka Jayanti, Rozzana Mohd Said
Methodology: Neti Eka Jayanti
Investigation: Rozzana Mohd Said.
Discssion of results: Neti Eka Jayanti, Rozzana Mohd Said.
Writing – Original Draft: Neti Eka Jayanti
Writing – Review and Editing: Rozzana Mohd Said.
Resources: Neti Eka Jayanti, Rozzana Mohd Said.
Supervision: Neti Eka Jayanti, Rozzana Mohd Said
Approval of the final text: Neti Eka Jayanti, Rozzana Mohd Said.

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