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Review

# Alloxan-induced diabetes, a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies

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ARTICLE INFO

*Article history:*
Received 14 September 2017
Accepted 8 February 2018
Available online xxx

*Keywords:*
Alloxan
Diabetes mellitus
Diabetogenic agent
Streptozotocin
Animals

ABSTRACT

Glycemic homeostasis refers to glucose balance or control within circulation in living organisms. It is normally and largely compromised in diabetes. The compromise when exacerbated, leads to several complications including retinopathy, nephropathy and neuropathy which are collectively known as diabetic complications and are the principal actors in co-morbidity and eventual mortality often associated with diabetes. The ability of therapeutic compounds including medicinal plants to restore glycemic balance or homeostasis in hyperglycemic condition is an index of their antidiabetic function and relevance. Alloxan and streptozotocin are the most popular diabetogenic agents used for assessing the antidiabetic or hypoglycemic capacity of test compounds. Notably, alloxan is far less expensive and more readily available than streptozotocin. On this ground, one will logically expect a preference for use of alloxan in experimental diabetes studies. Surprisingly, a sub meta-analysis of randomly selected studies conducted within the last one and half decade revealed otherwise. This observation necessitated the review of alloxan as a diabetogenic agent in animal studies.



## 1. Introduction

Alloxan which is chemically known as 5,5-dihydroxyl pyrimidine-2,4,6-trione is an organic compound, a urea derivative, a carcinogen and cytotoxic glucose analog [1]. The compound has the molecular formulae, $C_4H_2N_2O_4$ and a relative molecular mass of 142.06. Alloxan is one of the common diabetogenic agents often used to assess the antidiabetic potential of both pure compounds and plant extracts in studies involving diabetes. Among the known diabetogenic agents which include dithizone, monosodium glutamate, gold thioglucose, high fructose load, high glucose load and anti-insulin serum; alloxan and streptozotocin (STZ) are the most widely used in diabetes studies. The current average cost of one gram of

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https://doi.org/10.1016/j.medici.2018.02.001

alloxan and STZ are respectively 1.5 and 200 US dollars respectively. Due to relative affordability and availability, one will logically expect that alloxan will be more used compared to STZ [2]. However, a literature survey and sub meta-analysis that we carried out on the use of both compounds in experimental diabetes studies conducted within the last one and half decade (2000–2016) suggested otherwise (Table 1). Analysis of the data obtained showed that 30.3% of the studies used alloxan while 57.9% made used of STZ as a diabetogenic agent, and others which used glucose, fructose and genetic diabetic mice constituted the remaining 11.8% (Table 1).

## 2. Alloxan-induced diabetes

Alloxan-induced diabetes is a form of insulin-dependent diabetes mellitus that occurs as a result of alloxan administration or injection to animals [78,79]. It has been successfully induced in a variety of animal species; rabbits, mice, rats, monkeys, cats and dogs [80,81]. Alloxan has been administered in single or multiple doses, through different routes (intraperitoneal, intravenous and subcutaneous); with single intraperitoneal administration apparently the most employed mode. The dosage of the drug also varies across studies, ranging between 90 and 200 mg/kg of body weight (BW), with 150 mg/kg BW being the most frequently used dosage. Animal species, route of administration and nutritional status have been considered to play a role in determining the dose of alloxan appropriate for induction of diabetes [2]. However, single intraperitoneal administration of the drug at 170–200 mg/kg BW appears to be most effective [2].

Alloxan was first isolated by Brugnatelli in 1818 and initially described by Frederick Wohler and Justin Liebig in 1838 [83]. Alloxan causes diabetes by a mechanism which basically involves partial degradation of the beta (β) cells of pancreatic islets and subsequent compromise in the quality and quantity of insulin produced by these cells. Its use as a diabetogenic drug in experimental animals was first reported by Dunn and McLetchie in their study in which they successfully induced diabetes in experimental rabbits [78]. Thereafter, several authors have used alloxan-induced diabetes model as a ''study tool'' to elucidate the pathophysiology of the disease and much more as a ''search engine'' for antidiabetic compounds with better therapeutic characteristics.

The model employs two distinct pathological effects which include selective inhibition of glucose-stimulated insulin secretion, and induced formation of reactive oxygen species (ROS) which promotes selective necrosis of beta cells of the pancreas. Both effects collectively result in a pathophysiological state of insulin-dependent diabetes or type 1-like diabetes mellitus in cells [78,84]. The former is associated with specific inhibition of a pancreatic glucose sensor enzyme, glucokinase by alloxan whereas the latter is rather connected with the redox cycling ability of alloxan which results in ROS generation. More importantly, both effects have been linked to the chemical properties of alloxan as well as its structure.

### 2.1. *Chemical features of alloxan and their contribution to its diabetogenicity*

The diabetogenicity of alloxan is underlined by its selective cellular uptake by beta cells of the pancreas and consequent

**Table 1 – Randomly selected experimental diabetic studies conducted within the last two decades (1995–2016).**

| Authors | Diabetogenic agent used | Authors | Diabetogenic agent used | Authors | Diabetogenic agent used |
|---|---|---|---|---|---|
| Kameswararao et al. [3] | Alloxan | Yadav et al. [28] | Fructose | Ighodaro et al. [53] | Alloxan |
| Pari and Saravanan [4] | Alloxan | Al-Azzawie and Alhamdani [29] | Alloxan | Nyomaan et al. [54] | STZ |
| Eidi et al. [5] | STZ | Verspoh et al. [30] | Glucose | Petchi et al. [55] | STZ |
| Maiti et al. [6] | STZ | Jaiswal et al. [31] | STZ | Akaladi et al. [56] | STZ |
| Gupta et al. [7] | STZ | Sunil et al. [32] | STZ | Olatunji et al. [57] | Fructose |
| Bagri et al. [8] | STZ | Jelodar et al. [33] | Alloxan | Daud et al. [58] | STZ |
| Tabuchi et al. [9] | STZ | Ighodaro et al. [34] | STZ | Cao et al. [59] | STZ |
| Ragavan and Krishnakumari [10] | Alloxan | Asgary et al. [35] | Alloxan | Saravanan et al. [60] | STZ |
| Dewanjee et al. [11] | Alloxan | Kumar et al. [36] | Alloxan | Hakkim et al. [61] | Alloxan |
| Yang et al. [12] | Alloxan | Venkatesh et al. [37] | Alloxan | Lee et al. [62] | STZ |
| Jala et al. [13] | Fructose | Paril et al. [38] | Alloxan | Poudyal et al. [63] | CHO/High fat |
| Jemai et al. [14] | Alloxan | Shanmugasundaram et al. [39] | Alloxan | Dzeufiet et al. [64] | STZ |
| Sridhar et al. [15] | STZ | Nugroho et al. [40] | Fructose | Anathan et al. [65] | Alloxan |
| Pandit et al. [16] | STZ | Jelastin et al. [41] | Alloxan | Miura et al. [66] | KK mice |
| Papato et al. [17] | STZ | Satheesh and Paril [42] | Alloxan | Oliveira et al. [67] | STZ |
| Zhang and Tan [18] | STZ | Wainstein et al. [43] | STZ | Singh et al. [68] | STZ |
| Sarkhail et al. [19] | STZ | Moon [44] | STZ | Bnouham et al. [69] | STZ |
| Habibuddin et al. [20] | STZ | Chung et al. [45] | STZ | Surana et al. [70] | Alloxan |
| Liu et al. [21] | STZ | Ahangarpour et al. [46] | Fructose | Anwar et al. [71] | STZ |
| Abdelmoaty et al. [22] | STZ | Prince et al. [47] | Alloxan | Ju et al. [72] | STZ |
| Oku et al. [23] | STZ | Abedinzade et al. [48] | STZ | Gandhi et al. [73] | STZ |
| Orhan et al. [24] | STZ | Kook et al. [49] | STZ | Shirwaikar et al. [74] | STZ |
| Ezquer et al. [25] | STZ | Kumar et al. [50] | STZ | Chen et al. [75] | STZ |
| Zhao et al. [26] | STZ | Shajeela et al. [51] | Alloxan | Djomeni et al. [76] | STZ |
| Singh et al. [27] | STZ | Sowmia and Kokilavani [52] | Alloxan | Veerapur et al. [77] | STZ |

STZ, streptozotocin.

Please cite this article in press as: Ighodaro OM, et al. Alloxan-induced diabetes, a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies. Medicina (2018), https://doi.org/10.1016/j.medici.2018.02.001