A New Stochastic Model to Find the Insulin Secretion from Human Islets Using Exponential Distribution

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Abstract:

Many plant based products have been suggested as potential antidiabetic agents, but few have been shown to be effective in treating the symptoms of Type 2 diabetes mellitus (T2DM) in human studies, and little is known of their mechanisms of action. The effects of a novel high molecular weight Gymnema sylvestre (GS) extract, Om Santal Adivasi (OSA) on plasma insulin, C-peptide and glucose in a small cohort of patients with T2DM are reported here. Oral administrationof OSA induced significant increases in circulating insulin and C-peptide, which were associated with significant reductions in fasting and post-prandial blood glucose. The results of insulin secretion from human islets of langerhans were compared using the marginal distribution of a stretched Brownian motion $B(t^{\alpha})$ using exponential distribution.

Key Words: Insulin Secretion, Type 2 Diabetes, Anomalous Diffusion, Brownian Motion & Exponential Distribution

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1. Introduction:

The most common pharmacological treatments for T2DM, sulphonylureas and biguanides, tend to lose their effectiveness with prolonged treatment duration, so new pharmacological agents have been developed, including peroxisome proliferator activated receptor-γ (PPARγ) agonists and agents that stimulate insulin secretion such as glucagon like peptide-1 (GLP-1) analogs and dipeptidyl peptidase IV (DPPIV) inhibitors [15]. However, the widespread application of these novel agents is limited by their cost and by concerns about their long term safety [19]. Herbal medicines have attracted attention as alternative therapeutic agents for treating T2DM because they are relatively inexpensive and many have been used for decades or centuries without deleterious side effects. However, while many plant based products have been suggested as potential antidiabetic agents, few have yet been shown to be effective in treating the symptoms of T2DM in humans, and their mechanisms of action are uncertain.

Gymnema sylvestre (GS) is a large woody climber plant, from the Asclepiadaceae family. This plant has been used in Ayurvedic medicine for the treatment of diabetes. Crude or low molecular weight GS extracts have been reported to have antidiabetic effects in alloxan or streptozotocin treated animals by raising plasma insulin levels and attenuating blood glucose responses during oral glucose/sucrose tolerance tests [7] & [18]. Similarly, crude or low molecular weight GS extracts have been reported to have hypoglycemic effects in patients with hyperglycemic diabetes [1] & [18]. The antihyperglycemic effect of GS extracts in these studies was postulated to be due, at least in part, to the ability of the plant leaves to increase insulin secretion from β-cells of the islets of Langerhans, although this was not directly demonstrated. Most biologically active compounds isolated from GS leaves have

relatively low molecular weights [13], and the previously documented glucose lowering activities of GS have been attributed to these low molecular weight components. Recently a high molecular weight GS extract was isolated which was subsequently designated as the Om Santal Adivasi (OSA) extracts after the Santal tribe who first used GS leaves in Ayurvedic medicine. The present study investigated the effects of insulin secretion from human islets.

The master equation approach to model anomalous diffusion is considered. Anomalous diffusion in complex media can be described as the result of superposition mechanism reflecting in homogeneity and non stationary properties of the medium. For instance, when this superposition is applied to the time fractional diffusion process, the resulting master equation emerges to be the governing equation of the Erdelyi Kober fractional diffusion, which describes the evolution of the marginal distribution of the Brownian motion, as

$$f_*(x;t) = \frac{1}{\sqrt{4\pi t^{\alpha}}} exp\left\{\frac{-x^2}{4t^{\alpha}}\right\}$$

This motion is a parametric class of stochastic processes that provides models for both fast and slow anomalous diffusion: it is made up of self similar processes with stationary increments and depends on two real parameters. The class includes the fractional Brownian motion, the time fractional diffusion stochastic processes, and the standard Brownian motion. In this frame work, the M-Wright function emerges as a natural generalization of the Gaussian distribution, recovering the same key role of the Gaussian density for the standard and the fractional Brownian motion.

2. Notations:

$T2DM$	-	Type 2 Diabetes Mellitus
GS	-	Gymnema Sylvestre
OSA	-	Om Santal Adivasi
$PPAR\gamma$	-	Peroxisome Proliferator Activated Receptor γ
$GLP1$	-	Glucagon Like Peptide-1
$DPPIV$	-	Dipeptidyl Peptidase IV
$D_1(x)$	-	Drift Coefficient
$D_2(x)$	-	Diffusion Coefficient
$F(x)$	-	External Force Field
$K(x,t)$	-	Integral Operator
$L_{\theta}^{-\theta}(\xi)$	-	Stable Density
$P(D,x,t)$	-	Spectrum of Values of D
$B_H(t)$	-	Brownian Motion
C_{α}	-	Dimension
t	-	Assuming Time
x	-	Scale Parameter

3. The Master Equation Approach:

Statistical description of diffusive processes can be performed both at the microscopic and at the macroscopic levels. The microscopic level description concerns the simulation of the particle trajectories by opportune stochastic models. Instead, the macroscopic level description requires the derivation of the evolution equation of the probability density function of the particle displacement (the Master Equation) which is, indeed, connected to the microscopic trajectories. The problem of microscopic and macroscopic descriptions of physical systems and their connection is addressed and discussed in a number of cases. The most common examples of this microscopic to macroscopic dualism are the Brownian motion process together with the standard diffusion equation and the Ornstein Uhlenbeck stochastic process with the Fokker Planck equation [3] & [16]. But the same coupling occurs for several applications of the random walk method at the microscopic level and the resulting

macroscopic description provided by the Master Equation for the probability density function [20].

In many diffusive phenomena, the classical flux gradient relationship does not hold. In these cases anomalous diffusion arises because of the presence of nonlocal and memory effects. In particular, the variance of the spreading particles does no longer grow linearly in time. Anomalous diffusion is referred to as fast diffusion, when the variance grows according to a power law with exponent greater than 1, and is referred to as slow diffusion; when that exponent is lower than 1. It is well known that a useful mathematical tool for the macroscopic investigation and description of anomalous diffusion is based on Fractional Calculus. A fractional differential approach has been successfully used for modelling purposes in several different disciplines, for example, statistical physics, neuroscience, economy and finance, control theory, and combustion science**.** Further applications of the fractional approach are recently introduced and discussed by [9].

Moreover, under a physical point of view, when there is no separation of time scale between the microscopic and the macroscopic level of the process, the randomness of the microscopic level is transmitted to the macroscopic level and the correct description of the macroscopic dynamics has to be in terms of the Fractional Calculus for the space variable [6]. On the other side, fractional integro / differential equations in the time variable are related to phenomena with fractal properties [17]. In this paper, the correspondence microscopic to macroscopic for anomalous diffusion is considered in the framework of the Fractional Calculus.

Making use of the grey noise theory, introduced a class of self similar stochastic processes termed grey Brownian motion. This class provides stochastic models for the slow anomalous diffusion and the corresponding Master Equation turns out to be the time fractional diffusion equation. This class of self similar processes has been extended to include stochastic models for both slow and fast anomalous diffusion and it is named generalized grey Brownian motion. Moreover, in a macroscopic framework, this larger class of self similar stochastic processes is characterized by a Master Equation that is a fractional differential equation in the Erdelyi Kober sense. For this reason, the resulting diffusion process is named Erdelyi Kober fractional diffusion [14].

4. The Master Equation and Its Generalization:

The equation governing the evolution in time of the probability density function (pdf) of particle displacement $P(x;t)$, where $x \in R$ is the location and $t \in R_0^+$ the observation instant, is named Master Equation (ME). The time t has to be interpreted as a parameter such that the normalization condition $\int P(x;t)dx = 1$ holds for any t. In this respect, the Master Equation approach describes the system under consideration at the macroscopic level because it is referred to as an ensemble of trajectories rather than a single trajectory. The most simple and more famous Master Equation is the parabolic diffusion equation which describes the normal diffusion. Normal diffusion, or Gaussian diffusion, is referred to as a Markovian stochastic process whose probability density function satisfies the Cauchy problem:

$$\frac{\partial P(x;t)}{\partial t} = D\frac{\partial^2 P(x;t)}{\partial x^2}, \quad P(x;0) = P_0(x) \tag{1}$$

where $D > 0$ is called diffusion coefficient and has physical dimension $[D] = L^2T^{-1}$. The fundamental solution of (1), also named Green function, corresponds to the case with initial condition $P(x;0) = P_0(x) = \delta(x)$ and turns out to be the Gaussian density:

$$f(x;t) = \frac{1}{\sqrt{4\pi Dt}} exp\left\{-\frac{x^2}{4Dt}\right\} \tag{2}$$

In this case, the distribution variance grows linearly in time, that is, $\langle x^2 \rangle = \int_{-\infty}^{+\infty} x^2 f(x;t)dx = 2Dt$. The Green function represents the propagator that allows to express a general solution through a convolution integral involving the initial condition $P(x;0) =$

$P_0(x)$, that is,

$$P(x;t) = \int_{-\infty}^{+\infty} f(\xi;t) P_0(x-\xi) d\xi$$

Diffusion equation (1) is a special case of the Fokker Planck equation [16]

$$\frac{\partial P}{\partial t} = \left(-\frac{\partial}{\partial x} D_1(x) + \frac{\partial^2}{\partial x^2} D_2(x) \right) P(x;t) \tag{3}$$

where coefficients $D_1(x)$ and $D_2(x) > 0$ are called drift and diffusion coefficients, respectively. The Fokker Planck equation, also known as Kolmogorov forward equation, emerges naturally in the context of Markovian stochastic diffusion processes and follows from the more general Chapman Kolmogorov equation [3], which also describes pure jump processes.

A non Markovian generalization can be obtained by introducing memory effects, which means, from a mathematical point of view, that the evolution operator on the right hand side of (3) depends also on time, that is,

$$\frac{\partial P}{\partial t} = \int_0^t \left[\frac{\partial}{\partial x} D_1(x, t-\tau) + \frac{\partial^2}{\partial x^2} D_2(x, t-\tau) \right] P(x;\tau) d\tau$$

A straight forward non Markovian generalization is obtained, for example, by describing a phase space process (v, x), where v stands for the particle velocity, as in the Kramers equation for the motion of particles with mass m in an external force field $F(x)$, that is,

$$\frac{\partial P}{\partial t} = \left[-\frac{\partial}{\partial x} v + \frac{\partial}{\partial v} \left(v - \frac{F(x)}{m} \right) + \frac{\partial^2}{\partial v^2} \right] P(v, x; t) \tag{4}$$

In fact, due to the temporal correlation of particle velocity, eliminating the velocity variable in (4) gives a non Markovian generalized ME of the following form [16]:

$$\frac{\partial P}{\partial t} = \int_0^t K(x, t-\tau) \frac{\partial^2}{\partial x^2} P(x;\tau) d\tau \tag{5}$$

where the memory kernel $K(x,t)$ may be an integral operator or contain differential operators with respect to x, or some other linear operator. If the memory kernel $K(x,t)$ were the Gelfand Shilov function

$$K(t) = \frac{t_+^{-\mu-1}}{\Gamma(-\mu)}, \quad 0 < \mu < 1$$

where the suffix $+$ is just denoting that the function is vanishing for $t < 0$, then ME (5) would be

$$\frac{\partial P}{\partial t} = \int_{0_-}^{t^+} \frac{(t-\tau)^{-\mu-1}}{\Gamma(-\mu)} \frac{\partial^2}{\partial x^2} P(x;\tau) d\tau = D_t^{\mu} \frac{\partial^2 P}{\partial x^2}$$

that is, the time fractional diffusion equation [9]. The operator D_t^{μ} is the Riemann Liouville fractional differential operator of order μ in its formal definition according to [5] and it is obtained by using the representation of the generalized derivative of order n of the Dirac delta distribution: $\delta^{(n)}(t) = t_+^{-n-1}/\Gamma(-n)$ with proper interpretation of the quotient as a limit if $t = 0$. It is here reminded that, for a sufficiently well behaved function $\varphi(t)$, the regularized Riemann Liouville fractional derivative of non integer order $\mu \in (n-1, n)$ is

$$D_t^{\mu} \varphi(t) = \frac{d^n}{dt^n} \left[\frac{1}{\Gamma(n-\mu)} \int_0^t \frac{\varphi(\tau) d\tau}{(t-\tau)^{\mu+1-n}} \right]$$

For any $\mu = n$ non negative integer, it is recovered the standard derivative

$$D_t^{\mu} \varphi(t) = \frac{d^n}{dt^n} \varphi(t)$$

Now consider a Physical Mechanism for Time Stretching Generalization, It is well known that the "Stretched" exponential $exp(-t^{\theta})$ with $t > 0$ and $0 < \theta < 1$, being a completely monotone function, can be written as a linear superposition of elementary exponential functions with different time scales T. This follow directly from the well known formula of the Laplace transform of the unilateral extreme stable density $L_{\theta}^{-\theta}(\xi)$ [11], that is,

$$\int_0^\infty e^{-t\xi} L_\theta^{-\theta}(\xi)d\xi = e^{-t^\theta}, \quad t > 0, \quad 0 < \theta < 1$$

Where

$$L_\theta^{-\theta}(\xi) = \frac{1}{\pi}\sum_{n=1}^{\infty} \frac{(-1)^{n-1}}{n!} \Gamma(1+n\theta)\sin(n\pi\theta)\xi^{-\theta n-1}$$

Putting $\xi = 1/T$, it follows that

$$\int_0^\infty e^{-t/T} L_\theta^{-\theta}\left(\frac{1}{T}\right)\frac{dT}{T^2} = e^{-t^\theta}, \quad t > 0, \quad 0 < \theta < 1 \tag{6}$$

and $T^{-2}L_\theta^{-\theta}(1/T)$ is the spectrum of time scales T.

In the framework of diffusion processes, the same superposition mechanism can be considered for the particle probability density function. In fact, anomalous diffusion that emerges in complex media can be interpreted as the resulting global effect of particles that along their trajectories have experienced a change in the values of one or more characteristic properties of the crossed medium, as, for instance, different values of the diffusion coefficient, that is, particles diffusing in a medium that is disorderly layered.

This mechanism can explain, for example, the origin of a time dependent diffusion coefficient. Consider, for instance, the case of a classical Gaussian diffusion (1) where different, but time independent, diffusion coefficients are experienced by the particles. In fact, let $\rho(D,x,t)$ be the spectrum of the values of D concerning an ensemble of Gaussian densities (2) which are solutions of (1), that is,

$$f(x;t,D) = \frac{1}{\sqrt{4\pi Dt}} exp\left(-\frac{x^2}{4Dt}\right) \tag{7}$$

where the dependence on the diffusion coefficient D is highlighted in the notation, then, taking care about physical dimensions, in analogy with (6):

$$\begin{aligned}\int f(x;t,D)\rho(D,x,t)dD &= \frac{1}{\sqrt{4\pi C_\alpha^{1-\alpha/2}t^\alpha}} exp\left\{-\frac{x^2}{4C_\alpha^{1-\alpha/2}t^\alpha}\right\} \\ &= f\left(x;\frac{C_\alpha^{1-\alpha/2}t^\alpha}{D_0}, D_0\right) \\ &= f_*(x;t)\end{aligned} \tag{8}$$

where $0 < \alpha < 2$, D_0 is a reference diffusion coefficient according to notation adopted in (7) and

$$\rho(D,x,t) = \frac{x^{2-4/\alpha}t^{3/2-\alpha/2}}{(4C_\alpha)^{1-2/\alpha}C_\alpha^{(1-\alpha/2)/2}D^{3/2}} L_{\alpha/2}^{-\alpha/2}\left[\frac{x^{2-4/\alpha}t}{(4C_\alpha)^{1-2/\alpha}D}\right]$$

Hence, the superposition mechanism corresponds to a "Time Stretching" in the Gaussian distribution of the form $t \to C_\alpha^{1-\alpha/2}\, t^\alpha/D_0$ and the additional parameter C_α has dimension: $[C_\alpha] = [L^2T^{-\alpha}]^{1/(1-\alpha/2)}$. From now on, in order to lighten the notation, it is set that $D_0 = 1$ and $C_\alpha = 1$. Note that the Gaussian probability density function in (8)**,** that now reads

$$f_*(x;t) = \frac{1}{\sqrt{4\pi t^\alpha}} exp\left(-\frac{x^2}{4t^\alpha}\right) \tag{9}$$

can be seen as the marginal distribution of a "Stretched" Brownian motion $B(t^\alpha)$. Such a process is actually a stochastic Markovian diffusion process and it is easy to understand that the "Anomalous" behavior of the variance comes from the power like time stretching. However, the Brownian motion stationarity of the increments is lost due to just the nonlinear time scaling. One can preserve the stationarity on the condition to drop the Markovian property. For instance, the probability density function given in (9) is also the marginal density function of a fractional Brownian motion $B_H(t)$ of order $H = \alpha/2$. Such a process is Gaussian, self similar, and with stationary increments.

5. Example:

Eleven patients (7 Female, 4 Male) were recruited and consented for an in vivo study of the effects of OSA administration on blood glucose and insulin levels. The mean age of the cohort was 50.1 ± 3 years (Female: 50.7 ± 4; Male: 49 ± 5, $p > 0.2$) with a range of 36–70

years. The mean body weight at the outset of the trial was 58.7 ± 7.6 kg (Female: 57.7 ± 3.0; Male: 60.5 ± 2.8, $p > 0.2$) with a range of 45–70 kg. Patients were either newly diagnosed with T2DM, or had previously been treated with standard pharmacological regimens. Exclusion criteria were pregnancy, pre-existing heart disease, hypertension or respiratory disorders, and failure of compliance with the protocol. OSA was administered orally in capsule form at a dose of 500 mg (2 × 250 mg capsules) two times each day before food intake for 60 days, giving a total daily dose of 1g OSA. Blood samples were taken at the start of the trial (day 0) and at the completion of the trial (day 60), and body weight was recorded at the start and completion of the trial. Blood glucose was estimated as described [12] and insulin and C-peptide were measured in serum samples by radioimmunoassay (RIA), as [2].

The effect of OSA on insulin secretion from human islets in vitro was examined using a multi channel, temperature controlled perifusion system, essentially as described previously [10]. The perifusion system consisted of 16 Swinnex chambers fitted with 1 μm nylon mesh filters. Islets within the chambers were perifused at a flow rate of 0.5 mL/min with a physiological buffer [4] supplemented with 2 mm $CaCl_2$, 2 mm glucose and 0.5 mg/mL BSA for 60 min to establish a stable basal rate of insulin secretion, after which perifusate samples were collected at 2 min intervals and stored at −20°C until assayed for insulin content by radioimmunoassay [8]. Since glucose induced insulin secretion is temperature dependent, all perifusion experiments were carried out in a temperature controlled room at 37°C.

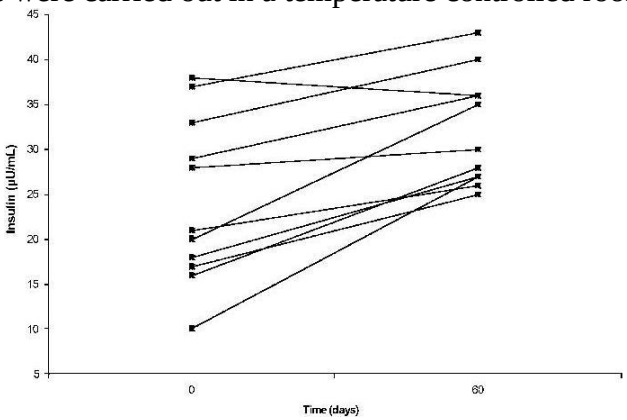

Figure (1): Effect of Daily Oral Administration of OSA on Plasma Insulin Secretion Levels from Human Islets with Type 2 Diabetes Mellitus

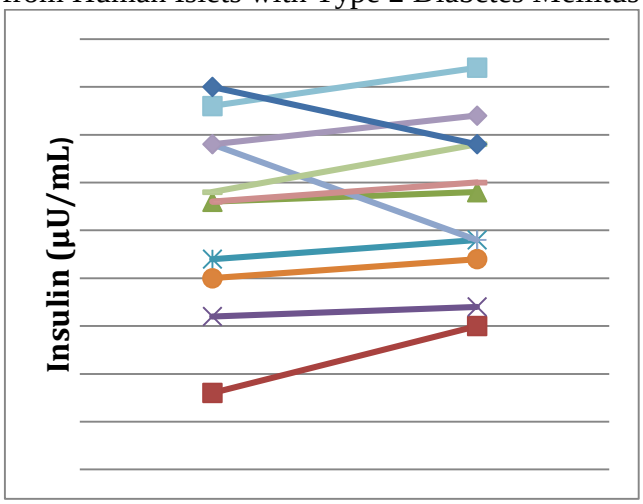

Figure (2): Effect of Daily Oral Administration of OSA on Plasma Insulin Secretion Levels from Human Islets with Type 2 Diabetes Mellitus Using Exponential Distribution.

6. Conclusion:

In summary, this is the first report showing that OSA, a high molecular weight fraction isolated from GS leaf extract is effective in reducing blood glucose and increasing plasma insulin and C-peptide levels in humans. Our parallel in vitro studies suggest that at least some of these effects of OSA can be attributed to a direct stimulatory effect on insulin secretion from islets of Langerhans. OSA may therefore provide a potential alternative therapy for the hyperglycemia associated with T2DM. The mathematical model also stresses the same effect of daily oral administration of OSA on plasma insulin secretion levels from human islets with type 2 diabetes mellitus. The medical report {Figure (1)} is beautifully fitted with the mathematical models {Figure (2)}; $(i.e)$ the results coincide with the mathematical and medical report.

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