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(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Renoprotective effect of *Capsicum annum* against ethanol-induced oxidative stress and renal apoptosis

Moumita Das¹ | Subhashree Basu² | Bhaswati Banerjee³ | Kuladip Jana³ | Anurupa Sen⁴ | Gouriprosad Datta¹

¹Department of Physiology, Rammohan College, Kolkata, India

²Department of Physiology, Tamralipta Mahavidyalaya, Tamluk, India

³Division of Molecular Medicine, Bose Institute, Kolkata, India

⁴Department of Physiology, City College, Kolkata, India

Correspondence

Gouriprosad Datta, Department of Physiology, Rammohan College, 85A, Raja Rammohan Sarani, Kolkata, West Bengal 700009, India.
Email: dattagp@yahoo.co.in

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Abstract

The present study explored the ameliorative potency of aqueous extract of *Capsicum annum* (AqCA), against oxidative imbalance and renal toxicity induced by ethanol. Randomly grouped male Wistar rats ($n = 6$), were marked as ethanol-treated (2 g/kg bw, i.p.), CA₁₂₅ (125 mg/kg bw, i.p.), CA₂₅₀ (250 mg/kg bw, i.p.), ethanol pre-treated with CA (similar doses), and control (0.5 ml normal saline, i.p.), and treated for 30 consecutive days. Biochemical analysis of tissue and serum parameters was performed, along with histopathological and histochemical studies. Also, we performed TUNEL assay and western blotting for our experimental groups. Statistical analysis revealed significant ($p \leq .001$) alteration in the levels of antioxidant enzymes, serum urea, creatinine, pro-inflammatory cytokines, and cleaved caspases, along with histopathological alterations in the ethanol-treated group. Prior treatment with AqCA prevented ethanol-induced alterations in tissue and serum parameters. These findings indicate that the extract of CA can protect renal cells from ethanol-induced damage by inhibiting oxidative stress, inflammatory response, and apoptosis.

Practical applications

Chronic alcohol consumption is a major public health concern that leads to various diseases and social problems as well. It affects both the affluent and non-affluent society equally. Alcohol (ethanol) is a renowned hepato-toxicant and a well-documented risk factor for oxidative stress, with less known effect on the kidney. Thus, it is essential to investigate the effect of alcohol metabolism on the kidney to find a remedy to prevent it. The present investigation depicts the anti-oxidative and anti-inflammatory role of *Capsicum annum* against ethanol-induced renal damage. The outcome of this study can be utilized in the future for phytotherapeutic herbal drug formulation. Besides, the bioactive components identified in the study can be further explored by researchers or pharmaceutical corporates for potential therapeutic purpose against renal impairment.

Abbreviations: AI, apoptotic index; BUN, blood urea nitrogen; CA, *Capsicum annum* L.; Caspase, cysteine aspartic acid-specific protease; Cont, control; Cu-Zn SOD, copper zinc superoxide dismutase; DAPI, 4, 6-diamidino-2-phenylindole; EtOH, ethanol; G6PD, glucose 6-phosphate dehydrogenase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; GST, glutathione-S-transferase; H-E, hematoxylin-eosin; IL-6, interleukin-6; MDA, malondialdehyde; Mn-SOD, manganese-superoxide dismutase; PBS, phosphate buffer saline; ROS, reactive oxygen species; SODs, superoxide dismutases; TBARS, thiobarbituric acid reactive substance; TNF- α , tumor necrosis factor- α ; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling.

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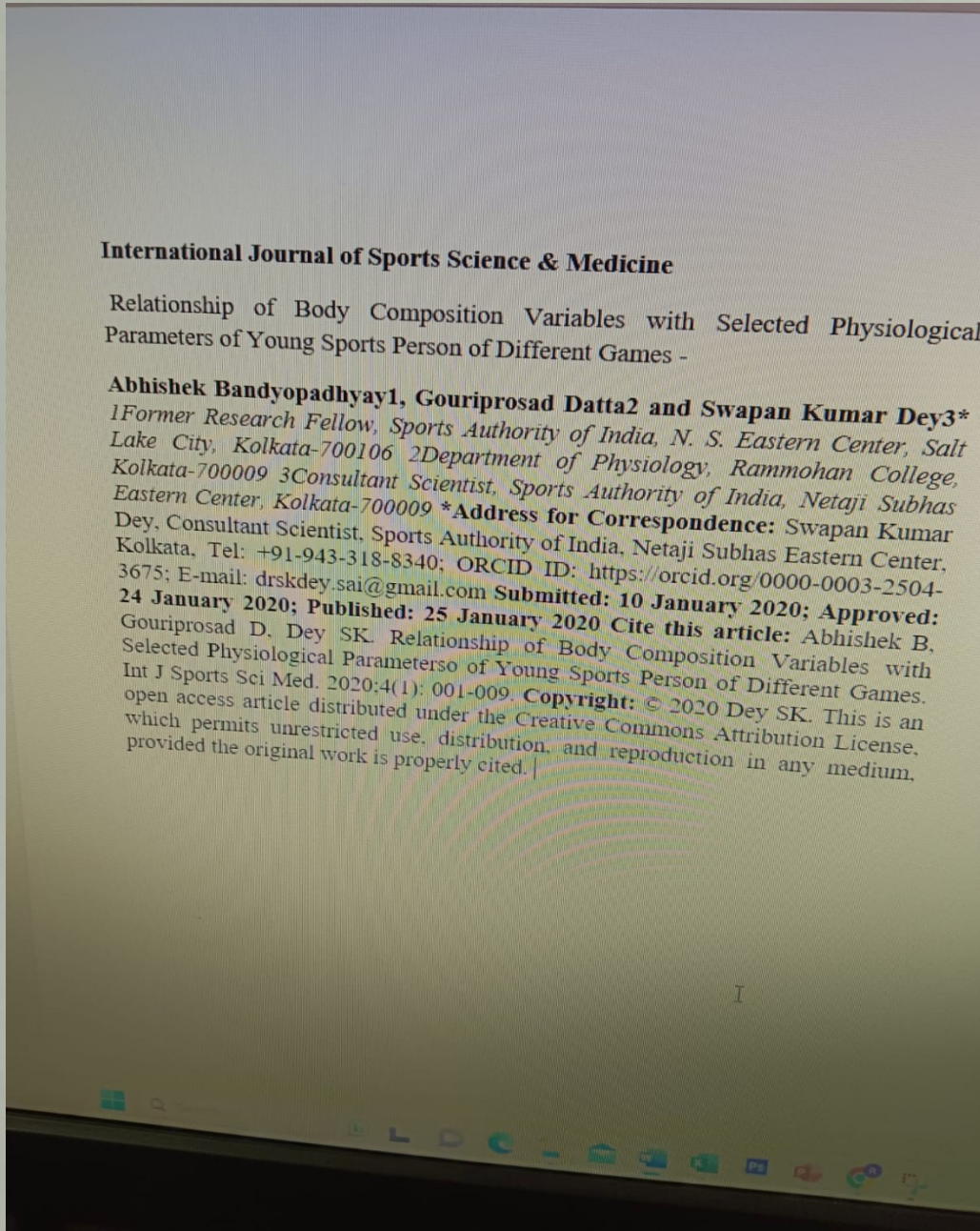
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Name of the teacher: Dr. Gouriprosad Datta

Title of paper: Relationship of Body Composition Variables with Selected Physiological Parameters of Young Sports Person of Different Games



S Sanyal

Principal
Rammohan College
Kolkata - 700009

Phone : 2350-5687
2354-3853
Fax : (033) 2350-5687



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102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Name of the teacher: Dr. Gouriprosad Datta

Title of paper: Effective Dose of Herbal Gold Nanoparticles for Protection of Acetaminophen-Induced Hepatotoxicity in Male Albino Rats

Effective Dose of Herbal Gold Nanoparticles for Protection of Acetaminophen-Induced Hepatotoxicity in Male Albino Rats

Mousumi Mitra, Amit Bandyopadhyay, Gouriprasad Datta & Dilip K Nandi

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E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Name of the teacher: Dr. Gouriprosad Datta

Title of paper: Nephroprotective effect of green synthesised gold nanoparticles using bark extract of Terminalia arjuna on acetaminophen induced nephrototoxicity in male albino rat

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Research Article

Nanotechnology for better drug targeting



Nephroprotective Effect of Green Synthesised Gold Nanoparticles Using Bark Extract of Terminalia Arjuna on Acetaminophen Induced Nephrotoxicity in Male Albino Rat

Mousumi Mitra¹, Amit Bandyopadhyay², Gouriprasad Datta³ and Dilip K Nandi^{1*}

¹PG Dept. of Human Physiology, Raja Narendra Lal Khan Women's College (Autonomous), Midnapore-721102, West Bengal.

²PG Dept. of Physiology, University of Calcutta, Kolkata, West Bengal, 700009.

³PG Dept. of Physiology, Rammohan College, 102/1, Raja Rammohan Sarani, Kolkata, West Bengal, 700009.

Abstract: Green synthesised gold nanoparticles offer a great promise in biomedicine. An overdose of acetaminophen causes severe hepatotoxicity and nephrotoxicity. The development of nephroprotective drugs through eco-friendly production routes is a major challenge for current pharmacology. This study was undertaken to examine the therapeutic effects of green synthesised gold nanoparticles (AuNPs) using aqueous bark extract of Terminalia arjuna, on acetaminophen induced nephrotoxicity in male albino rats and also to select the most effective dose of AuNPs to protect from nephrotoxicity. Terminalia arjuna, is a herbal plant of high interest in Asian traditional medicine. The bark of this tree has been widely used in the preparation of ayurvedic formulations such as powerful cardiotoxic, antioxidative, antiuremic and antimicrobial properties. In this study 36 experimental albino rats were taken and randomly divided into 6 groups. Group 1 served as normal control. Group 2 received acetaminophen intraperitoneally at concentration of 500mg/kg of body weight for 14 days and Groups 3,4,5,6 were co-administered with acetaminophen (500mg/kg/day) along with AuNPs at doses 55, 175, 550, 2000 µg/kg/day intraperitoneally for 14 days. After 14 days all animals were sacrificed for biochemical and histopathological studies. Among different experimental doses of AuNPs (55,175,550, 2000µg/kg/day), 175µg/kg/day showed more potent activity towards biochemical indices and histopathological studies. There was significant (p<0.05) increase in Urea, Creatinine, CRP and MDA levels but significant decrease in SOD, CAT and GSH activity in acetaminophen treated group, in comparison to control group but co-administration with AuNPs (175µg/kg/day) restored the activities of these biochemical markers and also of the antioxidant enzymes. Hence, this study confirmed that AuNPs at dose 175µg/kg/day have better nephroprotective efficacy.

Keywords: Acetaminophen, Antioxidant, Biochemical indices, Nephrotoxicity, Terminalia arjuna.

*Corresponding Author

Dilip K Nandi^{1*}, PG Dept. of Human Physiology, Raja Narendra Lal Khan Women's College (Autonomous), Midnapore-721102, West Bengal.



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E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Name of the teacher: Dr. Debapriya Das

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Regular Article

Nonlinear response of a parametric bistable oscillator with multiple excitations

Somnathi Roy¹, Debapriya Das², and Dhruva Banerjee^{1,*}

¹ Department of Physics, Jadavpur University, Kolkata, India
² Rammohan College, Kolkata, India

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Abstract. We study the nonlinear response of a certain parametrically driven bistable oscillator that is subjected to two external periodic drives of widely different frequencies. We observe prominent resonant response, both analytically and numerically, when the effective frequency of the system is tuned close to the frequency of the slow drive, the tuning parameter being solely the strength of the high frequency drive.

1 Introduction

Studies on enhanced response of a trapped system to a low frequency field as a consequence of the presence of some rapidly varying excitation has been a subject of extensive investigation during the last four decades. The excitation can be either of a random nature represented by some additive or multiplicative noise, or of a deterministic nature realizable by a high frequency periodic forcing. In the former case, the widely addressed field of stochastic resonance has played a central role in revealing interesting physics of bistable [1,2], monostable [3,4] and excitable [5,6] classical as well as quantum [7,8] systems. In the latter case, the phenomenon of vibrational resonance gained prominence from the work of Landa and McClintock [9] following which theoretical [11,12], numerical [13] as well as experimental [14,15] works with special emphasis on nonlinear systems [16–25] have been extensively pursued.

Among a wide variety of nonlinear systems, those with parametric excitations have been an important subject of study ever since Michael Faraday observed – as early as in 1831 – that the surface wave of a fluid filled cylinder, excited vertically, had the time period twice that of its own natural oscillation. Since then a plethora of work encompassing all disciplines of natural sciences as well as engineering have been carried out [26–33]. The response, stable or unstable, of a system subjected to parametric excitation is sensitively dependent on the values of the parameters involved and endeavors for proper understanding of the stability characteristics of such oscillators have led to developments of rich methods in perturbation theory and dynamical systems in general.

However, it appears that apart from a few recent works [34–37], investigations of the behavior of parametric oscillators in the backdrop of vibrational resonance have not

been that extensive. In this paper we study a parametric bistable oscillator subjected to a combination of slow and rapid frequency forcing and find out, using perturbation theory, how the system responds nonlinearly to the slow drive as one varies the strength of the fast-frequency excitation. In Section 2 we describe the model and the rationale behind its consideration. In Section 3 we go into detailed mathematical considerations followed by numerical simulations in Section 4. Satisfactory agreement is observed between the analytical and numerical results. The paper is concluded in Section 5.

2 The model

The oscillator we shall study in this paper has three forcing functions operative simultaneously. The setting of a typical problem pertaining to the phenomenon of vibrational resonance, as has been alluded to in the Introduction, has two forcing frequencies at play where one is much larger in magnitude than the other. Usually, the role of the higher forcing frequency is to catalyze the resonant response of the system to the lower forcing frequency over wider ranges. These frequencies are considered in a different footing from the natural frequency of the oscillator. The objective of the present paper is to bring in a periodic variation in the natural frequency of the oscillator with a frequency that coincides with the lower forcing frequency just mentioned above. The equation of such a parametrically driven oscillator looks like

$$\ddot{x} + \gamma \dot{x} - \omega_0^2(1 + q \cos \omega_p t)x + \alpha x^3 = c \cos \omega t + g \cos \Omega t \quad (1)$$

where $c \cos \omega t$ is the term denoting the lower frequency drive while $g \cos \Omega t$ represents the higher frequency drive and, as stated above, the parametric frequency ω_p is equal

* e-mail: dhruva_iacs@gmail.com

S Sanyal

Principal
Rammohan College
Kolkata - 700009



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Name of the teacher: Dr. Biswanath Banerjee

Title of paper: Science, A Metaphor of Nationalism: A P C Ray and Postcoloniality

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Science, a Metaphor of Nationalism: Acharya Prafulla Chandra Ray and Postcoloniality

Biswanath Banerjee

Abstract

The scientific and intellectual Renaissance of Bengal in the late nineteenth and early twentieth century had acted as a major force in the triumph of independence of India and its progress towards a modern civilization. In the history of this new scientific awakening Acharya Prafulla Chandra Ray (1861-1944) occupies a significant position who realized the importance of science as integral to nationalist consciousness and nation building. Ray envisioned science to be a common concern of all humankind which was to be integrated with the development of a public use of reason and the emergence of Indian Nationalism through the establishment of national industry. In this paper my endeavour will be to locate Acharya Prafulla Chandra, not only as a scientist but also as an industrialist, a social thinker, an educationist and a cultural theorist who played a significant role in the social reformation, moral regeneration, economic development and political emancipation of India. In scrutinizing the corpus of Ray's writings on science, industry and society, I shall try to trace a consistent postcolonial strain in Ray that used the tools of mimicry and imitation to challenge the colonial apparatus.

Keywords: Nationalism, Postcoloniality, Acharya Prafulla Chandra Ray.

I can assure you, however, dear sister, that in serving my favourite science I have only one idea in my mind, namely, that through her I should serve my country. Our aspirations are the same. God knows, I have no other object in my life. (Ray, 1932 & 1935, p. 233)

In the late nineteenth and early twentieth century, India witnessed a steady progress and development of science, which was largely inspired by the British colonial expansion and its imperial practices. The deployment of science by the British as a facilitator of colonial rule generated a corresponding interest in science among the Western educated indigenous intelligentsia. These intellectuals and scientists sought to cultivate and utilize the knowledge of science and technology in constructing the concept of nationhood and to challenge the colonial apparatus. Among these leading scientists of India, Acharya Prafulla Chandra Ray (1861-1944) was one of the most important figures. Challenging the Western hegemony over science and rationality, Ray conceived of science and its practices as a universal phenomenon and claimed India's active participation in the enterprise of modern science, which would eventually serve as an effective weapon against colonialism.



This chapter has attempted to trace a consistent postcolonial strain in the vast corpus

REDMI 9 POWER

S Sanyal

Principal
Rammohan College
Kolkata - 700009

Phone : 2350-5687
2354-3853
Fax : (033) 2350-5687



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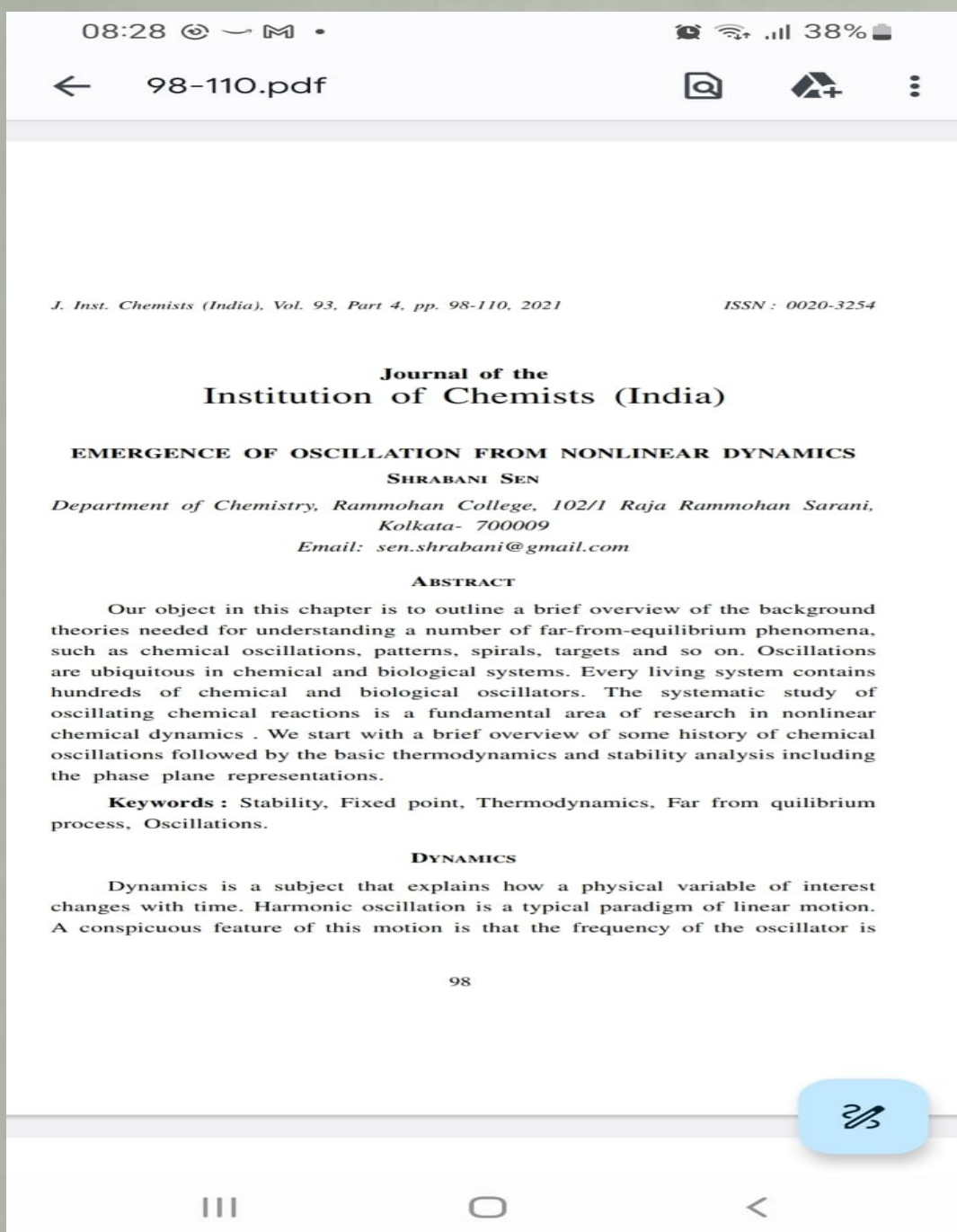
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Name of the teacher: Dr. Shrabani Sen

Title of paper: Emergence of Oscillation from Nonlinear Dynamics.



S Sanyal

Principal
Rammohan College
Kolkata - 700009



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(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Name of the teacher: Dr. Bhuban Chandra Das

Title of paper: Soret-Dufour magneto-thermal radiative convective heat and mass transfer of chemically and thermally stratified micropolar fluid over a vertical stretching/shrinking surface in a porous medium



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Soret-Dufour magneto-thermal radiative convective heat and mass transfer of chemically and thermally stratified micropolar fluid over a vertical stretching/shrinking surface in a porous medium

Dulal Pal & Bhuban Chandra Das

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E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Name of the teacher: Dr. Samarendra Nath Banerjee
Title of paper: Carcinogenic and Mutagenic Effects of Betel Nut with Haematological, Histopathological and Cytological Toxicity in Solid Tumour Bearing Mouse

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International Journal of Pharmacognosy and Phytochemical Research 2021; 13(4),12-21
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Research Article

Carcinogenic and Mutagenic Effects of Betel Nut with Haematological, Histopathological and Cytological Toxicity in Solid Tumour Bearing Mouse

Sudipta Chowdhury and Samarendra Nath Banerjee*

Department of Zoology, Rammohan College, 102/1 Raja Rammohan Sarani, Kolkata-700009, West Bengal, India

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ABSTRACT
The aim of the present study is to evaluate how ethanolic betel nut extract (BNE) at different doses influences the tumour growth rate on solid tumour bearing Swiss albino mouse along with haematological, histopathological and cytogenetical toxicity. In addition, the nature of vascular density of tumour has also been studied morphometrically to investigate the angiogenic effect of BNE. A solid tumour was induced on leg for experiment. After five days of tumour cell inoculation ethanolic BNE was injected intraperitoneally on alternating days. The solid tumour growth gradually increased with the steady increase of tumour vascularisation with increasing concentrations of BNE treatment. A steady decrease in the haemoglobin percentage and total RBC count along with lymphocyte population was noted with the steady increase in the WBC count and neutrophil population. Moreover, BNE at the different concentrations induces significant genetic damage i.e. chromosomal aberration in bone marrow cells and histopathological abnormalities in liver in solid tumour bearing mice. Therefore, our present studies indicate that ethanolic betel nut extract causes significantly mutagenic, carcinogenic and angiogenic effects on solid tumour bearing mice.
Keywords: Betel nut extract, Sarcoma 180, Solid tumour, RBC, WBC, Chromosome, Angiogenesis

INTRODUCTION
The growth of new blood vessels from the pre-existing vasculature is the main driving force in initiation and development of tumour and determines the metastatic potential. The blood vessel supports the tumour growth by supplying passage of oxygen and nutrients.^{1,2} Epidemiological studies revealed that consumption of smoked fish, meat, wild mushroom and different types of plant products such as leaves and seeds of *Lathyrus sativus* are associated with different types of diseases including cancer.³⁻⁴ So, the potential hazard of its wide application cannot be ignored. The experiments since the last few decades have generated evidence that betel nut acts as a genotoxic and carcinogenic agent in animals as well as humans. Earlier studies have been carried out to know the genotoxic and cytotoxic potential of BNE: on different in vivo and in vitro cell systems considering chromosome aberration and SCE studies.⁵ Our preliminary studies revealed that BNE plays a substantial role in the development of solid tumour growth in mouse which was analysed morphometrically.⁶ Therefore, the present study has been oriented to carry out a thorough analysis on solid tumour in Swiss albino male mice in response to BNE considering the growth rate with tumour vasculature, haematological toxicity, histopathological particularly hepatotoxicity and cytological toxicity for better understanding of mutagenic, carcinogenic and angiogenic effect.

MATERIALS AND METHODS

Collection and Extraction of betel nut
Ethanolic betel nut was prepared with some modifications of the methodology originally described by earlier researchers.^{3,7,8} Fresh betel nut was purchased and authenticated by Botanical survey of India, Botanical Garden, Howrah, West Bengal, India. 100gm of betel nuts were processed into small pieces and kept in 90% ethanol overnight for extraction. The solution of betel nut was then placed into the thimble of a Soxhlet and the extraction process was continued for 48 hours. The ethanolic solution was filtered twice and dried in an incubator at 50°C. Then the dried mass of BNE was kept for future use.

Experimental animals
Nine-week-old healthy Swiss male albino mice (*Mus musculus*) and weighing about 20gm were used for the present experiment. The mice were acclimatized in the experimental room under controlled condition of temperature (24°C - 26 °C) and humidity. The animals were fed sterilised food pellets and water *ad libitum*. The experiments were carried out in accordance with the rules and guidelines formulated by the Institutional Animal Ethics Committee (Animal House Registration No. - 1795 / PO / Bre / S/ 14 CPCSEA- 31/12/2014), Rammohan College, Kolkata, for maintenance and care of laboratory animals.

Selection of animal tumour model and tumour transplantation
Sarcoma 180 (S-180) murine ascitic tumour cell lines were maintained *in vivo* by serial intraperitoneal transplantation in the laboratory. The solid tumour was generated by

*Author for Correspondence: samban2kcal@yahoo.com

S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

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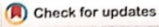
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(RESEARCH ARTICLE) 

Genotoxic activity of betel nut on germinal cell in Sarcoma 180 ascites tumour bearing male mice

Sudipta Chowdhury and Samarendra Nath Banerjee*

Department of Zoology, Rammohan College, 102/1 Raja Rammohan Sarani, Kolkata-700009, West Bengal, India.

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Abstract

The genotoxicity of the ethanolic extract of betel nut was evaluated using sarcoma 180 tumour bearing mouse considering sperm motility, sperm viability, biochemical estimation of fructose in seminal fluid and sperm head morphology assays. Sperm head morphology was studied by H-E staining and Toluidine blue staining method. But Toluidine blue staining method is a reliable method to evaluate the DNA damage of sperms. Ethanolic BNE (betel nut extract) can suppress the percentage of sperm motility, sperm viability and seminal fructose level. In addition, it can also enhance the percentage of DNA damaged sperms. Moreover, histological sections of testes have been studied in control and BNE treated sarcoma 180 tumour bearing mice to highlight the potential toxic effect of BNE. The significant decreasing rate of seminal fructose concentration, sperm motility as well as viability and increasing rate of sperm head abnormality in different doses of treated series may be as a result of different toxic alkaloid ingredients present in BNE. Therefore, the results showed the potential of the BNE to induce different types of germ cell abnormalities in tumour bearing male mice.

Keywords: Betel nut extract; Sarcoma 180; Seminal fructose; Seminiferous tubule; Sperm abnormality; Viable cell

1. Introduction

The analysis of semen and sperm chromatin abnormalities has been studied extensively for predicting male fertility [1]. Different types of biochemical components have been found in seminal fluid [2]. Fructose - the most important carbohydrate is found among different biochemical substances that acts as a donor of energy to the spermatozoa [3,4]. Low level of seminal fructose is positively correlated with low seminal fluid volume and low sperm motility [5]. So, fructose is essential for normal growth of sperm head morphology, sperm viability and motility. It is well known that exposure to some plant products cause different physiological as well as cytological abnormalities in experimental animals [6]. Areca nut or betel nut is used to treat different types of disorders such as leprosy, cold, worm infection and leukoderma in ancient period [7]. Now a day, betel nut is very popular as it is consumed by people of India and other Asian countries. The genotoxicity and carcinogenicity of betel nut extract was reported by earlier researchers [8]. Research since last four decades has generated enough evidence to involve betel nut, as a carcinogen in human [9,10,11]. Moreover, the high incidence of oral, oesophagus, liver, stomach and pancreas cancer has been associated with the habit of betel nut chewing [11,12,13,14]. Several studies have also suggested that betel nut extract can enhance the chromosomal aberration rate of mice in vivo system [15,16]. Betel nut treated experimental male mice showed low percentage of sperm viability and motility [17]. Our earlier studies have demonstrated that betel nut significantly enhanced the sperm head abnormality with steady decrease of sperm motility, haemoglobin percentage, and total count of RBC and survival rate of normal Swiss albino mice [17]. But detailed study about the effect of betel nut extracts in sarcoma 180 tumour bearing mouse is insufficient with respect to semen and germinal cell abnormality. The present study has therefore, been oriented to evaluate the dose dependent effect of BNEs on seminal fluid and germinal cell of

* Corresponding author: Samarendra Nath Banerjee; E-mail: samban2kcal@yahoo.com
Department of Zoology, Rammohan College, 102/1 Raja Rammohan Sarani, Kolkata-700009, West Bengal, India.
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Principal
Rammohan College
Kolkata - 700009



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(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

Accredited B++ Grade by NAAC

Ref.

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Name of the teacher: Dr. Samarendra Nath Banerjee
Title of paper: Anti-mutagenic activity of pomegranate extract and 2-methoxyestradiol in combination on Swiss Albino mouse - *Mus musculus*.

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ANTIMUTAGENIC ACTIVITY OF POMEGRANATE EXTRACT AND 2 - METHOXY-ESTRADIOL IN COMBINATION ON SWISS ALBINO MOUSE - *MUS MUSCULAS*

Anasua Banerjee and Samarendra Nath Banerjee *

Department of Zoology, Rammohan College, 102/1 Raja Rammohan Sarani, Kolkata - 700009, West Bengal, India.

Keywords:
Pomegranate extracts, 2-Methoxyestradiol, Chromosomal aberration, Survivability, Haemoglobin


Correspondence to Author:
Dr. Samarendra Nath Banerjee
Associate Professor,
Department of Zoology,
Rammohan College, 102/1 Raja Rammohan Sarani, Kolkata - 700009, West Bengal, India.
E-mail: samban2kcal@yahoo.com

ABSTRACT: Pomegranate extracts (PGEs) exhibit antioxidative, antiproliferative, and antineoplastic activities. 2-Methoxyestradiol (2-ME), the end metabolite of 17 β estradiol (E2), an antiangiogenic agent, inhibits tumor growth. Our earlier investigations demonstrated that aqueous PG extract (PGE) in combination with 2-ME showed antineoplastic effect on Sarcoma-180 tumor cells. The present paper has been oriented to evaluate the antimutagenic or anticlastogenic effect of PGE in combination with 2-ME on normal Swiss albino mice. A comparative evaluation of the antioxidant potential and free radical scavenging activity of ethanolic and aqueous extracts of PG was evaluated by total phenol, flavonoid and Ferric reducing antioxidant power assay (FRAP) content as well as 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity. Ethanolic extract showed more amounts of phenolic compounds, which is a good sign of high antioxidative potentiality. The aqueous extract has high flavonoid content, which dominates the phenolic activity of the ethanolic extract. The aqueous extract has high Ferric reducing power with more scavenging activity in DPPH assay, which promotes the extract to give a protective property. Present results demonstrated that combination effects of aqueous PGE (400 mg/kg of body weight) and 2-ME (1.5 mg/kg of body weight) significantly protect the mouse from cellular and hematological toxicity. This study introduces a novel combination, where the particular combination of PG and 2-ME (*i.e.* 400 mg/kg of body weight + 1.5 mg/kg of body weight) not only enhances the survivability of mouse synergistically, but also inhibits the cytological and hematological toxicity antagonistically, as analyzed by Chou Talalay method, which could serve as an antimutagenic potential.

INTRODUCTION: The anti-mutagenic, anti-diabetic, anti-carcinogenic, and anti-oxidative potentiality of different plants has been reported by many authors¹⁻⁸. Different types of bioactive compounds (*i.e.*, phenol, indole, selenium, flavonoid, ellagitannin, ellagic acid, ascorbic acid, *etc.*) are present in fruits and vegetables, can inhibit different types of diseases by blocking metabolic activities through detoxification⁸⁻¹¹.

The whole plant extract (methanolic) of *Cleome gynandra* (capparidaceae), commonly known as 'Hurhur' and 'Karaila' in India, is used for the treatment of tumors and antiinflammatory actions¹².

Crude methanolic extract from the pericarp of *Garcinia mangostana* (family: Guttiferae) has shown antiproliferative, apoptotic, and antioxidative properties against some human breast cancer cell lines¹³. Ginger- *Zingiber officinale* (Zingiberaceae) extract has a preventive property against different neoplastic diseases because of the potent activity of polyphenolic and flavonoid compounds¹⁴. Moreover, the mutagenic potentiality of plant extract has also been reported¹⁵. Pomegranate, one of the important and oldest

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S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

Accredited B++ Grade by NAAC

Ref.

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Name of the teacher: Dr. Md Ahmadullah

Title of paper: Common fixed point theorems under an implicit contractive condition on metric spaces endowed with an arbitrary binary relation and an application

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Common fixed point theorems under an implicit contractive condition on metric spaces endowed with an arbitrary binary relation and an application

Md Ahmadullah*, Mohammad Imdad† and Mohammad Arif‡
Department of Mathematics, Aligarh Muslim University
Aligarh-202002, U.P., India
*ahmadullah201@gmail.com
†mhimdad@gmail.com
‡mohdarif154c@gmail.com

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The aim of this paper is to establish some metrical coincidence and common fixed point theorems with an arbitrary relation under an implicit contractive condition which is general enough to cover a multitude of well-known contraction conditions in one go besides yielding several new ones. We also provide an example to demonstrate the generality of our results over several well-known corresponding results of the existing literature. Finally, we utilize our results to prove an existence theorem for ensuring the solution of an integral equation.

Keywords: Complete metric spaces; binary relations; contraction mappings; fixed point.

AMS Subject Classification: 47H10, 54H25

1. Introduction

The origin of metric fixed point theory is solely attributed to classical Banach contraction principle which was originated in the Ph.D. thesis of Banach in 1920. This work was later published in the form of a research paper [11] in 1922 which has already earned around 2000 google citations. The strength of Banach contraction principle lies in its applications which fall within the several domain such as: Functional Analysis, General Topology, Algebraic Topology, Differential Equation,

*Corresponding author.

S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

Accredited B++ Grade by NAAC

Ref.

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ORIGINAL RESEARCH PAPER



Invariant means on weakly almost periodic functions and generalized fixed point properties

Ahmed H. Soliman¹ · Mohammad Imdad² · Md Ahmadullah^{2,3}

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Abstract

In this paper, we prove common fixed point theorems for Generalized Suzuki Contractions (abbreviated as GSC) involving two semi-topological semigroups of self-mappings S_1 and S_2 , besides establishing the existence of a left invariant mean (abbreviated as LIM) on the space of all weakly almost periodic functions on $S_1 \cap S_2$ (abbreviated as $WAP(S_1 \cap S_2)$).

Keywords Fixed point property · Generalized non-expansive mapping · Suzuki contraction · Weakly compact convex set · Weakly almost periodic function · Reversible semigroup · Invariant mean

Mathematics Subject Classification 43A60 · 43A07 · 47H10 · 47H20

1 Introduction

Let E be a Banach space and C a nonempty bounded closed convex subset of E . A mapping $T : C \rightarrow C$ is said to be *non-expansive* if

✉ Mohammad Imdad
mhimdad@gmail.com
Ahmed H. Soliman
ahsoliman@gmail.com
Md Ahmadullah
ahmadullah2201@gmail.com

¹ Department of Mathematics, King Khaled University, Abha 9004, Saudi Arabia

² Department of Mathematics, Aligarh Muslim University, Aligarh, UP 202002, India

³ Present Address: Department of Mathematics, Rammohan College, Calcutta University, Kolkata, WB 700009, India

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RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Ref.

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Name of the teacher: Dr. Samiran Mondal

Title of paper: Exploring the efficacy of naturally occurring biflavone based antioxidants towards the inhibition of the SARS-CoV-2 spike glycoprotein mediated membrane fusion

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Exploring the efficacy of naturally occurring biflavone based antioxidants towards the inhibition of the SARS-CoV-2 spike glycoprotein mediated membrane fusion

Samiran Mondal ^{a,*}, Abhijit Karmakar ^b, Tamanna Mallick ^b, Naznin Ara Begum ^b

^a Department of Chemistry, Rammohan College, 102/1-Raja Rammohan Sarani, Kolkata, 700009, West Bengal, India
^b Department of Chemistry, Visva-Bharati (Central University), Santiniketan, 731 235, India

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ABSTRACT

Molecular docking studies were done to show the inhibitory effect of two naturally occurring biflavone based anti-HIV agents, hinokiflavone and robustiflavone against the SARS-CoV-2 spike (S) protein mediated attack on the human ACE2 receptors via membrane fusion mechanism. Nefamostat, a FDA approved drug, well-known as a serine protease inhibitor for MERS-CoV infection, was used as the reference compound. Both the biflavones, showed potential as inhibitors for SARS-CoV-2 S protein-mediated viral entry. The binding affinities of these naturally occurring biflavones for RBD-S2 subunit protein of SARS-CoV-2 were explored for the first time. Such binding affinities play a critical role in the virus-cell membrane fusion process. These biflavones are able to interact more strongly with the residues of heptad repeat 1 and 2 (HR1 and HR2) regions of S2 protein of SARS-CoV-2 compared to nefamostat, and thus, these biflavones can effectively block the formation of six-helix bundle core fusion structure (6-HB) leading to the inhibition of virus-target cell-membrane fusion.

1. Introduction

By the end of 2019, scientists came to know about a novel Corona virus, SARS-CoV-2 [Severe Acute Respiratory Syndrome-Corona virus-2] causing COVID-19 (Corona Virus Disease-19). This initially affected people of Wuhan city of China. Later, this virus became the root cause of deaths and untold sufferings of millions of people around the globe due to the unavailability of specific medicine/vaccine or therapeutic strategies.

Corona viruses (CoVs) are a family of RNA viruses, responsible for mild as well as a range of severe respiratory disease outbreaks and epidemics in human in last two decades e.g. Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (World Health Organization, 2019; Masters, 2006; Corman et al., 2019; Lu et al., 2015; WHO, 2004; WHO, 2016). Like, SARS-CoV and MERS-CoV, the very deadly SARS-CoV-2 belongs to β genus of CoVs containing positive-strand RNA (Wu et al., 2020). The size of the genome of SARS-CoV-2 falls in the range of ~30 kb involving 6 to 11 open ring frames (ORFs) (Song et al., 2019). Approximately, 67% of the entire genome is mainly located in the first ORF (ORF1a/ORF1b) which processes two polyproteins, pp1a and pp1ab and also encodes 16–17 non-structural proteins (NSPs) e.g. 3-chymotrypsin-like protease (3CL^{pro}), papain-like protease (PL^{pro}), helicase and RNA-dependent RNA polymerase (RdRp) (Dömling and Gao, 2020). The remaining ORFs encode accessory and structural proteins (Cui et al., 2019). Though SARS-CoV-2 genome has large size (characteristic of RNA virus), it genome encodes for fewer structural proteins; among which four major structural proteins are worth of mentioning: the structural spike (S) glycoprotein, small envelop (E) protein, nucleocapsid (N) protein and membrane (M) protein. These are essential for reproduction of a structurally complete virus particle (Dömling and Gao, 2020).

The spike (S) glycoprotein of CoVs, is responsible for the crown-like shape of the virus (Scheme 1 (a)) and belong to class-I viral fusion proteins, which facilitates the viral entry process into host cells through the binding with the receptors of the host cells, host tropism and pathogenesis (Lu et al., 2015; Millet and Whittaker, 2014). The binding of viral S protein through its receptor-binding domain (RBD) to the host cells instigates various vital steps necessary for viral infections e.g. fusion of viral and host membranes (Li, 2016; Zhu et al., 2018). The S proteins attacks the angiotensin-converting enzyme2 (ACE2) receptors of the host via its RBD and triggers a cascade of inflammation in the lower respiratory tract (Ksiazek et al., 2003; Kuba et al., 2005). Trimeric

* Corresponding author.
E-mail address: samiran@rammohancollege.ac.in (S. Mondal).

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S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

Accredited B++ Grade by NAAC

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Name of the teacher: Dr. Samiran Mondal

Title of paper: Phf5a regulates DNA repair in class switch recombination via p400 and histone H2A variants deposition

Article



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Phf5a regulates DNA repair in class switch recombination via p400 and histone H2A variant deposition

Nasim A Begum¹, Farazul Haque¹, Andre Stanlie^{1,2}, Afzal Husain^{1,3}, Samiran Mondal^{1,4}, Mikiyo Nakata¹, Takako Taniguchi⁵, Hisaaki Taniguchi⁵ & Tasuku Honjo^{1,*}

Abstract

Antibody class switch recombination (CSR) is a locus-specific genomic rearrangement mediated by switch (S) region transcription, activation-induced cytidine deaminase (AID)-induced DNA breaks, and their resolution by non-homologous end joining (NHEJ)-mediated DNA repair. Due to the complex nature of the recombination process, numerous cofactors are intimately involved, making it important to identify rate-limiting factors that impact on DNA breaking and/or repair. Using an siRNA-based loss-of-function screen of genes predicted to encode PHD zinc-finger-motif proteins, we identify the splicing factor Phf5a/Sf3b14b as a novel modulator of the DNA repair step of CSR. Loss of Phf5a severely impairs AID-induced recombination, but does not perturb DNA breaks and somatic hypermutation. Phf5a regulates NHEJ-dependent DNA repair by preserving chromatin integrity to elicit optimal DNA damage response and subsequent recruitment of NHEJ factors at the S region. Phf5a stabilizes the p400 histone chaperone complex at the locus, which in turn promotes deposition of H2A variant such as H2AX and H2A.Z that are critical for the early DNA damage response and NHEJ, respectively. Depletion of Phf5a or p400 blocks the repair of both AID- and I-SceI-induced DNA double-strand breaks, supporting an important contribution of this axis to programmed as well as aberrant recombination.

Keywords CSR; genomic instability; H2A.Z; NHEJ; Phf5a

Subject Categories DNA Replication, Recombination & Repair; Immunology

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Introduction

In mature B cells, activation-induced cytidine deaminase (AID) induces DNA breaks at the IgH locus in order to diversify the

antibody gene locus via somatic hypermutation (SHM) and class switch recombination (CSR) (Muramatsu *et al.*, 2000; Muramatsu *et al.*, 2007). The cellular DNA repair system plays a key role during these events as the DNA breaks at the variable and the switch (S) regions are processed distinctly, leading to SHM and CSR, respectively. In particular, CSR requires an elaborate DNA repair process to join the two S region DNA double-strand break (DSB) ends. The acceptor and the donor S regions, which are located several kilobases apart, are brought into proximity and undergo ligation predominantly mediated by non-homologous end joining (NHEJ) (Stavnezzer *et al.*, 2010; Boboila *et al.*, 2012a). However, genomic loci other than IgH are often mis-targeted by AID, and the repair of these DNA breaks by NHEJ is a potential source of oncogenic mutations and chromosomal translocations. Therefore, CSR and the associated genomic instability provide a unique opportunity to investigate DNA break-repair pathway and its regulation.

Active chromatin marks and their combinatorial histone codes are known to be involved in AID-induced genomic instability (Daniel *et al.*, 2010; Begum & Honjo, 2012; Li *et al.*, 2013; Sheppard *et al.*, 2018). Specific histone chaperones and transcription elongation complexes play important roles in the chromatin organization and histone modification regulation at the IgH locus (Pavri *et al.*, 2010; Stanlie *et al.*, 2010; Stanlie *et al.*, 2012). Moreover, several chromatin reader proteins, such as 53BP1, Brd4, and PTP1, are also known to promote DNA repair step of CSR (Reina-San-Martin *et al.*, 2007; Daniel *et al.*, 2010; Stanlie *et al.*, 2014). Thus, the chromatin-associated proteins involved in recognizing and/or remodeling the histone codes at the S regions can greatly impact CSR efficiency by influencing the DSB formation and/or recombination. For example, CSR requires histone post-translational modification H3K4me3, which promotes AID-induced DNA break in the recombining S regions. On the other hand, transcription elongation-associated FACT, SPT6, and DSIF complexes play a critical role in regulating H3K4me3 in the S regions. Therefore, deficiencies not only in FACT or SPT6, but also in any proteins involved in H3K4me3 formation

1 Department of Immunology and Genomic Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

2 BioMedicine Design, Pfizer Inc., Cambridge, MA, USA

3 Department of Biochemistry, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, India

4 Department of Chemistry, Rammohan College, Kolkata, India

5 Division of Disease Proteomics, Institute for Enzyme Research, University of Tokushima, Tokushima, Japan

*Corresponding author. Tel: +81 75 753 4371; Fax: +81 75 753 4388; E-mail: honjo@mfour.med.kyoto-u.ac.jp

S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

Accredited B++ Grade by NAAC

Ref.

Year 2021

Date 20

Name of the teacher: Dr. Samiran Mondal

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Article

Exploring the Propensities of Fluorescent Carbazole Analogs toward the Inhibition of Amyloid Aggregation in Type 2 Diabetes: An Experimental and Theoretical Endeavor

Tamanna Mallick, Abhijit Karmakar, Alpana Mukhuty, Chandrani Fouzder, Jishu Mandal, Samiran Mondal, Anup Pramanik, Rakesh Kundu, and Naznin Ara Begum*

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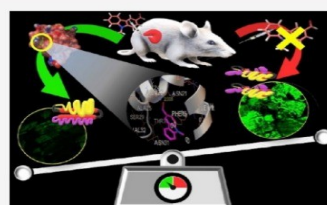
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ABSTRACT: Amyloid aggregation is a pathological trait observed in many incurable and fatal neurodegenerative and metabolic diseases associated with misfolding and self-assembly of various proteins. Noncovalent interactions between these structural motifs and small molecules can, however, prevent this aggregation. Herein, five structurally different synthetic (Cz1–Cz4) and naturally occurring (Cz5, mahanimbine) fluorescent carbazole analogs are explored for their comparative amyloid aggregation inhibitory activities. Cz3 inhibited the amyloid deposition on the pancreatic β -cells of diabetic mice. Moreover, Cz3 and Cz5 also showed efficacy as the fluorescent cell (MIN6) imaging agents. Further structural modifications of these carbazoles may lead to development of low-cost and non-toxic therapeutic agents for Type 2 diabetes and other amyloidosis-related diseases.



INTRODUCTION

Amyloid aggregation is a pathological trait observed in more than 30 serious neurodegenerative and metabolic diseases in human beings, e.g., Alzheimer's disease (AD), Parkinson's disease, Type 2 diabetes, etc.^{1–4} Misfolding and self-assembly of a wide range of proteins with little structural similarity in their primary sequence give rise to highly ordered (β -sheet rich) toxic fibrillar assemblies, known as amyloid aggregation.^{3,4} There is a quest for the novel therapeutic approaches, which can specifically target amyloid aggregation and delay or prevent its propagation.

Over the years, large numbers of research are being carried out to shed light on the etiology of Type 2 diabetes. Islet amyloid polypeptide (IAPP) or amylin is co-secreted with insulin from the pancreatic β -cells, and along with the insulin, it plays an important role in controlling blood glucose levels.^{5–9} However, apart from the body's insulin resistance, the misfolding of IAPP (triggered by factors like cellular oxidative stress, mitochondrial dysfunction, chromatin condensation, etc.) is considered as one of the key factors of Type 2 diabetes. The extracellular deposition of amyloid fibrils of IAPP on pancreatic β -cells causes their dysfunction.^{5,6,10–12} On the other hand, hyperinsulinemia is associated with Type 2 diabetes and other than IAPP, amyloids in the islet cells can also be formed by the excess secretion of insulin, which is amyloidogenic in nature.^{6,13–16} Thus, the identification of the external agents that can delay and prohibit the islet amyloid

aggregation can be a potential therapeutic strategy for Type 2 diabetes.^{7,8}

Nowadays, small molecules of natural product origin (secondary metabolites) with remarkable structural diversity, intense biological activities, and reduced toxicity are showing efficacy in preventing the aggregation of various amyloidogenic proteins, viz., A β , IAPP, TTR, etc.^{5,10,17–20} In this connection, it is noteworthy that carbazoles have attracted great attention as A β amyloid aggregation inhibitors.^{21–25} However, extensive studies on their activity toward the inhibition/prevention of islet amyloid aggregation are still rare;²⁶ despite this, several carbazole analogs, especially the carbazole alkaloids like mahanine, koenidine, and mahanimbine, isolated from the leaves of the plant *Murraya koenigii* Spreng. (commonly known as Indian Curry Leaf plant, Fam. Rutaceae), showed efficacy as antidiabetic agents in *in vitro* and in mice model.^{27,28} These naturally occurring carbazoles also showed efficiency toward the improvement of insulin resistance, i.e., activation of the insulin-stimulated glucose uptake pathway to control glucose homeostasis.^{27–29}

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S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

Accredited B++ Grade by NAAC

Ref.

Year 2021

Date 20

Name of the teacher: Dr. Shantanu Das

Title of paper: Endocrine Disruptor—A threat to the animal world.

Endocrine Disruptor—A threat to the animal world

Diptatanu Das

Department of Biological Sciences, Indian Institute of Science Education and Research, Kolkata, Mohanpur, Nadia, West Bengal, India

Shantanu Das

Department of Zoology, Rammohan College, 102/1 Raja Rammohan Sarani, Kolkata-700009, West Bengal, India

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Keywords: Ecology, endocrine disruptor, human health, phytoestrogen, xenoestrogen

Abstract

Various types of naturally occurring and artificially made chemicals cause disruption of endocrine processes among animals. They mimic biochemically with hormones and interfere with the normal signaling and activity of the endocrine system, causing enormous changes at the cellular level of animals from lower to higher organisms, including human being. These modified regulations of cellular activities as a result of endocrine disruptors have severe implications at the organismal level. Types and adverse effects of these natural and synthetic agents, especially estrogenic

S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

Accredited B++ Grade by NAAC

Ref.

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Name of the teacher: Dr. Sahana Mazumder Sen

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Review Article

Microbiology for Health Care



An Early Year History of Emergence of Multidrug-Resistant *Staphylococcus aureus* in West Bengal: A Review

Kartik Shaw^{1*} and Sahana Mazumder²

¹Research Scholar, Department of Physiology, Rammohan College, University of Calcutta, Kolkata, India

²Associate Professor, Department of Physiology, Rammohan College, University of Calcutta, Kolkata, India

Abstract: *Staphylococcus aureus* has been recognized as a causative agent of human diseases for more than 100 years. *Staphylococcus aureus* can cause numerous fatal diseases including sepsis, soft tissue injury, urinary tract infection. Emergence of multidrug resistance in *Staphylococcus aureus* is a very common problem worldwide. Multidrug resistant (MDR) bacterium can be identified if the strain is non-susceptible against at least one antibiotic agent in three or more antimicrobial categories. Multidrug resistant *Staphylococcus aureus* are becoming resistant against various antibiotics like azithromycin, clarithromycin, clindamycin, gentamicin, amikacin, imipenem and other β -lactam antibiotics. Resistance against methicillin and vancomycin can be said as methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Staphylococcus aureus* (VISA) respectively. However, 11% to 56% of the available *Staphylococcus aureus* are methicillin resistant in West Bengal. Whereas, the emergence of VISA was found to be equally high in this geographical region. Vancomycin resistant *Staphylococcus aureus* infections is too hard to treat, as vancomycin is said to be the last resort of antibiotics to treat methicillin resistant *Staphylococcus aureus*. These emergence of resistance against several antibiotics may include many ways like inhibition of drug entry into the cell, inactivation of β -lactamase enzyme, etc. several genes are also responsible for the drug resistance like *mecA*, *vanH*, *vanA* and *vanX*. The present review article deals with the research done on the antibiogram of *Staphylococcus aureus* within the last decade in West Bengal. It also puts light on the various methods by which the *Staphylococcus aureus* might become resistant against antibiotics and also tries to deal with the genetics involved in it.

Keywords: *Staphylococcus*, MRSA, VISA, Methicillin, Vancomycin, Multidrug.

*Corresponding Author

Kartik Shaw, Research Scholar, Department of Physiology,
Rammohan College, University of Calcutta, Kolkata, India



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S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Early Universe in view of a modified theory of gravity

Ranajit Mandal¹, Dalia Saha², Mohosin Alam³ and Abhik Kumar Sanyal^{2,*}

¹ Department of Physics, Rammohan College, Kolkata, West Bengal 700009, India

² Department of Physics, Jangipur College, Murshidabad, West Bengal 742213, India

³ Department of Physics, Saidpur U. N. H. S., Murshidabad, West Bengal 742225, India

E-mail: ranajitmandalphys@gmail.com, daliasahamandal1983@gmail.com, alammohosin@gmail.com and sanyal_ak@yahoo.com

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Abstract

We study the quantum evolution of the early Universe, its semi-classical analogue together with inflationary regime, in view of a generalized modified theory of gravity. The action is built by supplementing the non-minimally coupled scalar-tensor theory of gravity with scalar curvature squared term and a Gauss-Bonnet-dilatonic coupled term. It is generalized, since all the parameters are treated as arbitrary functions of the scalar field. It is interesting to explore the fact that instead of considering additional flow parameters, an effective potential serves the purpose of finding inflationary parameters. The dilaton stabilization issue appears here as a problem with reheating. Addition of a cosmological constant term alleviates the problem, and inflation is effectively driven by the vacuum energy density. Thus Gauss-Bonnet term might play a significant role in describing late-time cosmic evolution.

Keywords: generalized action, early Universe, canonical quantization, inflation

(Some figures may appear in colour only in the online journal)

1. Introduction

It is well known fact that the 'standard model of cosmology' based on general theory of relativity (GTR) explains a long evolution history of the Universe, right from the structure formation, and the formation of CMBR (at a redshift $z \approx 3200$) up to the recent decelerated matter dominated era (at a redshift $z \approx 1$), once the seed of perturbations is assumed to exist. Nevertheless, it has already been established that gauge-invariant divergences make GTR non-renormalizable, and also that it can not quite accommodate observations in connection $S_n I_a$

* Author to whom any correspondence should be addressed.

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S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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Conflict between some higher-order curvature invariant terms

Dalia Saha^a, Mohosin Alam^b, Ranajit Mandal^c, Abhik Kumar Sanyal^{a,*}

^a Dept. of Physics, Jangipur College, Murshidabad, West Bengal, 742213, India

^b Dept. of Physics, Saidpur U. N. H. S., Murshidabad, West Bengal 742225, India

^c Dept. of Physics, Rammohan College, Kolkata, West Bengal 700009, India

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Abstract

A viable quantum theory does not allow curvature invariant terms of different higher orders to be accommodated in the gravitational action. We show that there is indeed a conflict between the curvature squared and Gauss-Bonnet squared terms from the point of view of hermiticity. This means one should choose either, in addition to the Einstein-Hilbert term, but never the two together. We explore early cosmic evolution with Gauss-Bonnet squared term.

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1. Introduction

The problem associated with bare cosmological constant and the absence of a scalar field in the late universe, motivated cosmologists to propose several curvature induced gravity models, for solving the cosmic puzzle encountered at the late-stage of cosmological evolution. In this context, $F(R, \mathcal{G})$ theory (R and \mathcal{G} are the Ricci scalar and the Gauss-Bonnet term respectively), has been studied largely in recent years, and therefore is one of the prevalent models. It is well-known that the Gauss-Bonnet term is topologically invariant in 4-dimension. Thus, contribution from such a term in the field equations requires dilatonic coupling. A dilaton-like scalar field

* Corresponding author.

E-mail addresses: daliasahamandal1983@gmail.com (D. Saha), alammosin@gmail.com (M. Alam), ranajitmandalphys@gmail.com (R. Mandal), sanyal_ak@yahoo.com (A.K. Sanyal).

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S Sanyal

Principal
Rammohan College
Kolkata - 700009



RAMMOHAN COLLEGE

(Formerly City College W. Dept.)

102/1, Raja Rammohan Sarani, Kolkata - 700 009

E-mail : rmc.tic85b@yahoo.in, rmc.principal@gmail.com

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ORIGINAL ARTICLE

Effect of high intensity interval training on antioxidant status, inflammatory response and muscle damage indices in endurance team male players



Surojit Sarkar^a, Monalisa Debnath^a, Moumita Das^{a,b}, Amit Bandyopadhyay^c, Swapan Kr Dey^d, Gouriprosad Datta^{a,*}

^a Department of Physiology, Rammohan College, Kolkata, India
^b Department of Applied Nutrition and Dietetics, Sister Nivedita University, Kolkata, India
^c Sports and Exercise Physiology Laboratory, Department of Physiology, University of Calcutta, University Colleges of Science and Technology, 92 APC Road, Kolkata 700009, India
^d Department of Sports Science, University of Calcutta, India

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KEYWORDS
Athletes;
Muscular damage;
Oxidative stress;
Sprint interval training

Abstract
Introduction: High-intensity interval training (HIIT) has previously been reported having the effect of training period on altering oxidant status, muscle damage and performance. The present study was aimed to understand and evaluate the adaptive response of 8 weeks HIIT on muscle damage indices, inflammatory markers, oxidative stress variables and physical fitness parameters.
Methods: Forty young endurance male players [i.e., football (n=20) and field hockey (n=20)] were recruited under two groups i.e., control and HIIT. 8 weeks long 3h/day of sprint-HIIT was intervened for thrice/week. HIIT workouts includes total 4 sets/session (divided into 2 phase × 2 sets × 2min) of all-out sprint workout (at 90–95% of HR_{max} with work: rest = 1:1). Muscle damage indices (CK and LDH), inflammatory markers (IL-6 and TNF-α), oxidative stress variables (MDA, SOD, GSH and GPx) and physical fitness variables (VO_{2max}, W_{peak} and VJ) were assessed via following standard protocols.
Result: The HIIT resulted to significantly (p < 0.001) increase BMI (1.1%), LDH (15.0%), CK (14.4%), cortisol (9.4%), IL-6 (15.7%), TNF-α (18.2%), MDA (29.5%), VO_{2max} (13.6%), W_{peak} (11.6%), VJ (11.2%) and GPx (0.4%) along with significant (p < 0.001) reduction in BF% (7.6%), SOD (11.1%), GSH (10.8%) content of athletes.

* Corresponding author.
E-mail address: dattagp@yahoo.co.in (G. Datta).

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S Sanyal

Principal
Rammohan College
Kolkata - 700009