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Exploring the Influence of an Antifungal Medication on Patients Receiving Oral Hypoglycemic Therapy: Investigating the Interplay Between Medications

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Shruti M Thakre[1], D. Veerendra Kumar[2], Anil Ahuja[3], Naziya Hamid[4], Anup R Thakre[5], Mohd. Shahid Khan[6], Hemant A Sawarkar[7], Lalchand Devhare[8]

[1]Dr. R. G. Bhoyar Institute of Pharmacy, Seloo, Wardha, Maharashtra, India
Email: Shrutithakre85@gmail.com
[2]Pratishta Institute of Pharmaceutical Sciences, Durajpally (V), Chivmela (M), Suryapet (D), Telangana.
[3]Institute of Pharmaceutical Sciences, Sanskriti University Mathura, India
ORCID ID: 0000-0002-2225-8892
[4]Department of Emergency Medicine, Santosh Medical College & Hospital, Ghaziabad, Uttar Pradesh, India.
[5]Priyadarshini J. L. College of Pharmacy, Nagpur, Maharashtra, India- 440016.
ORCID ID: 0000-0001-5504-2230
[6]Maharishi Arvind International Institute of Pharmacy, Kota, Rajasthan, India.
[7]Anuradha College of Pharmacy, Sakegaon Road, Chikhli, Buldhana, Maharashtra, India.
[8]School of Pharmacy, G H Raisoni University, Saikheda, Chhindwara, Madhya Pradesh.

Corresponding Author: Lalchand D Devhare*

Email: lalchand.devhare@gmail.com
ORCID ID: 0000-0003-0579-4949

Keywords

Interaction; Pioglitazone; Repaglinide; Glucose, hypoglycemia

Abstract

In situations where diabetic patients who are prescribed either pioglitazone or repaglinide may also require treatment with an antifungal medication such as Itraconazole. In order to explore the potential interactions between Itraconazole and oral anti-diabetic agents, this study was carried out. Whole study was divided in 3 phases and blood glucose level (BGL) was measured. In the study, it was found that there are changes in BGL in normal and diabetic animals when concurrently used with itraconazole which may be due to at metabolic stage. The observed potentiation of hypoglycemic effects of both pioglitazone and repaglinide by itraconazole pre-treatment can be attributed to pharmacokinetic modification by Itraconazole.

1. Introduction

Individuals with diabetes mellitus (DM) may prone to many infections[1-3]. The underlying factors contributing to these effects involve poorly understood impairments in cell-mediated immunity and phagocyte functions. Additionally, reduced vascularization also plays a role in these observed outcomes. Due to compromised immunity, DM patients may suffer from fungal infections.[4] Some documents revealed about occurrence of fungal infections[5-8] in diabetics like mucormycosis[9-10], candidiasis[11-12], onychomycosis[13-18] etc. Reports signify that diabetics are on average suffer by fungi.[4,19-20].

Itraconazole is advised as it shows broad spectrum of activity. As per various evidences, several drugs modify the hypoglycemic activity of repaglinide and pioglitazone[21]. Itraconazole -antifungal drug reported to reduce CYP3A4 and little/less effect on CYP1A2, CYP2C9 and CYP2C8[22]. Pioglitazone is metabolized by isoenzyme CYP2C8 and CYP3A4 and somewhat extent by CYP2C9[23-24]. Further another oral antidiabetic agent repaglinide is reported to metabolize by CYP3A4 and CYP2C8[25]. Therefore there is possibility of interaction.[30-54].

2. Materials and Methods

2.1 Animals

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All the experimental animals were acclimatized under standard conditions.

2.2 Induction of diabetes

Male Wistar rats subjected to make diabetic by streptozotocin (STZ) 65 mg/kg, i.p. The STZ-treated rats exhibited noteworthy glycosuria and hyperglycemia. Confirmation of diabetes made by measuring fasting BGL 96 hours post-STZ injection. Rats with BGL exceeding 200 mg/dL were considered diabetic.

2.3 Blood and serum sample collection:

It was collected by suitable method of withdrawal. Serum obtained by centrifuging the blood for 10 min at 5000rpm.[26-28].

2.4 Estimation of blood glucose level (BGL)

BGL estimated by GOD/POD method[29].

2.5 Experimental procedure

2.5.1 Persuade of Itraconazole on BGL in normal albino rats (NAR)

Itraconazole-3.6 mg/kg p.o. bis in die/ week.

On the 7th day, 6 hours later of itraconazole, rats fasted for 18 hrs.

On the 8th day, the blood collected and tested.

2.5.2 Consequence of Itraconazole on pioglitazone and repaglinide in NAR

Rats received: pioglitazone 270 µg/kg/p.o or repaglinide 72 µg/kg/p.o. Blood taken at predefined time span.

Rats received: Itraconazole 3.6 mg/kg p.o bis in die -7 days.

On the 7th day, 6 hours after administration of itraconazole, the rats fasted for 18 hours

On 8th day blood collected to determine fasting BGL

Itraconazole (3.6 mg/kg p.o. bis in die/p.o) to all the animals.

After 60minutes, pioglitazone (270µg/kg/p.o) or repaglinide (72 µg/kg/p.o) was given.

2.5.3 Influence of Itraconazole on BGL in normal albino rabbits (NARt)

Same procedure was followed as 2.5.1 for rabbits.

2.5.4 Consequence of Itraconazole on pioglitazone and repaglinide in NARt

Same procedure was followed as 2.5.2 for rabbits.

2.5.5 Effect of Itraconazole on pioglitazone and repaglinide in diabetic rats (DR)

The DR received suspension of pioglitazone (270µg/kg/p.o) or repaglinide (72µg/kg/p.o) and blood collected.

In the next part :All the DR faced Itraconazole 3.6 mg/kg p.o./bis in die/week.

On 7th day, 6 hours of itraconazole, fasted for 18hours.

On 8th day, Itraconazole 3.6 mg/kg p.o./bis in die to all animals.

After 60 minutes, pioglitazone (270µg/kg) or repaglinide (72µg/kg) given.

Blood samples were collected in predefined intervals.

$$\% \text{ Blood glucose reduction at time 't'} = \frac{A-B}{A} \times 100$$

Where, A = Initial BGL

B = BGL after the drug administration.

3. Results and Discussion:

Due to polypharmacy, and need of multidrugs to treat so many diseases, patients have risk of various drug interactions. Sometimes co-administered drug may have narrow therapeutic window. Here, patients suffering from DM may have fungal infection also. In these cases, drugs like itraconazole having broad spectrum are prescribed. But there are reports who claims that, these co-administered drugs have interaction which may produce serious adverse effects.[21] In present study, when itraconazole was administered with pioglitazone or repaglinide in normal and diabetic animals, there was enhanced

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hypoglycemic effect. The results revealed that, normal and diabetic animals have significant BGL reduction.

Repaglinide treated animals, displayed hypoglycemic convulsions & remaning showed some signs of hypoglycemia. So, there is possibility of pharmacokinetic type of interaction among selected drugs.

Pioglitazone is metabolized by microsomal isoenzymes- CYP2C8, CYP3A4 and to lesser extent by CYP2C9 and repaglinide by the CYP2C8 and CYP3A4[23-25]. Documented reports divulge that, study drug Itraconazole is an inhibitor of CYP enzymes[22].

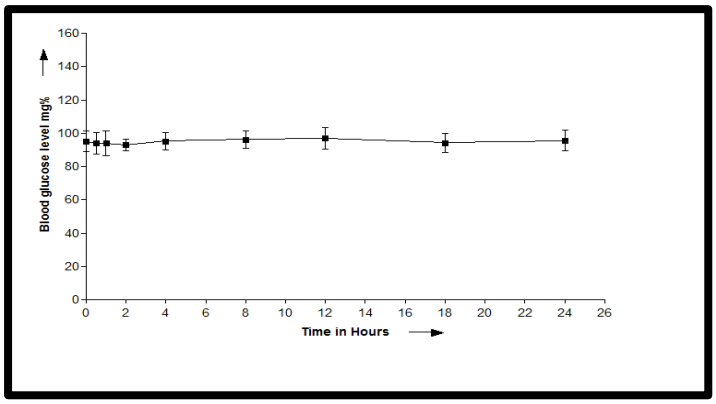

Figure 01: BGL (mg%) with Itraconazole in NAR

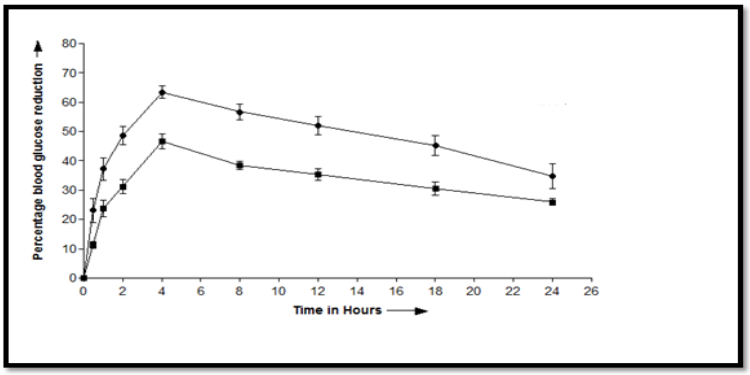

Figure 02: % BGL with pioglitazone before and after itraconazole treatment in NAR

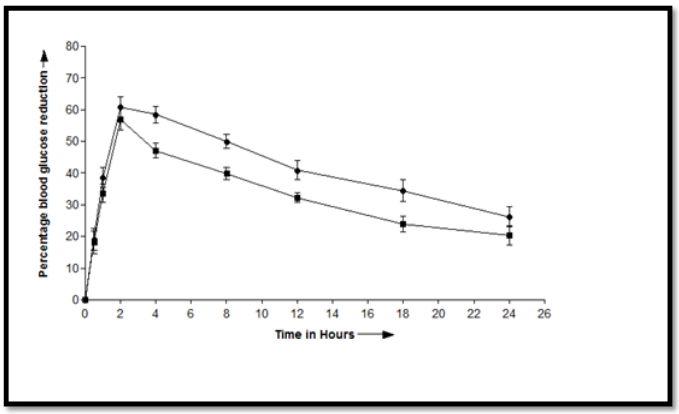

Figure 03: % BGL with repaglinide before and after itraconazole treatment in NAR

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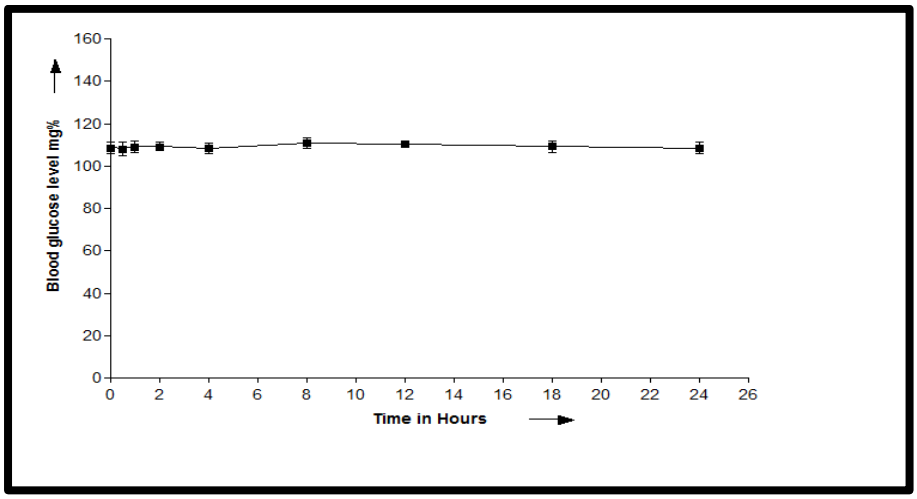

Figure 04: BGL (mg%) with Itraconazole in NAR

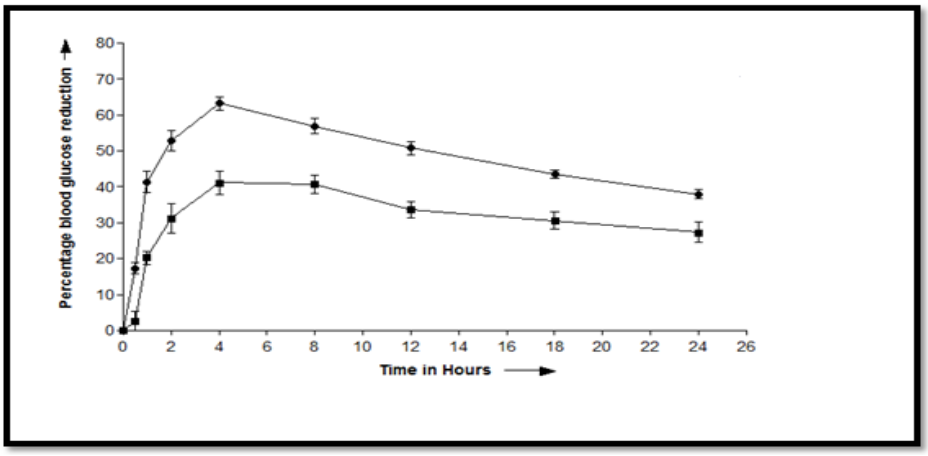

Figure 05: % BGL with pioglitazone before and after itraconazole treatment in NAR

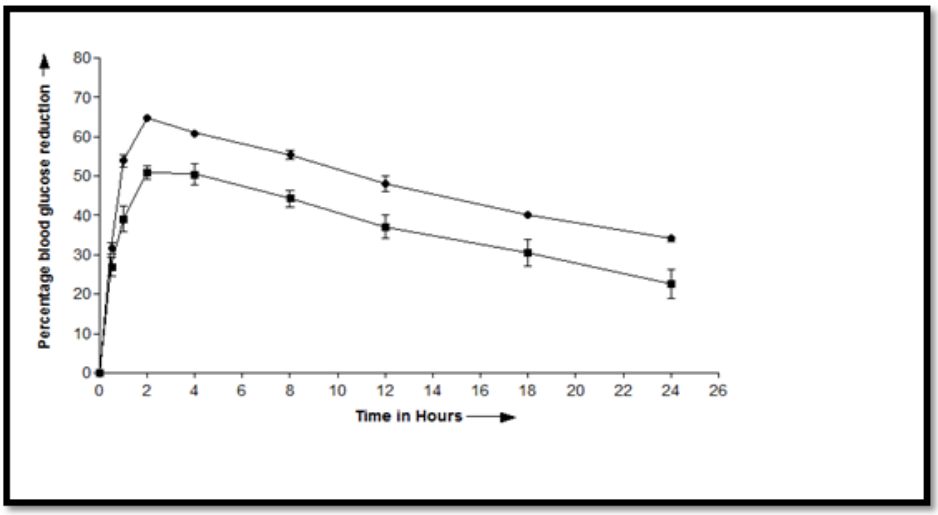

Figure 06: % BGL with Repaglinide before and after itraconazole treatment in NARt

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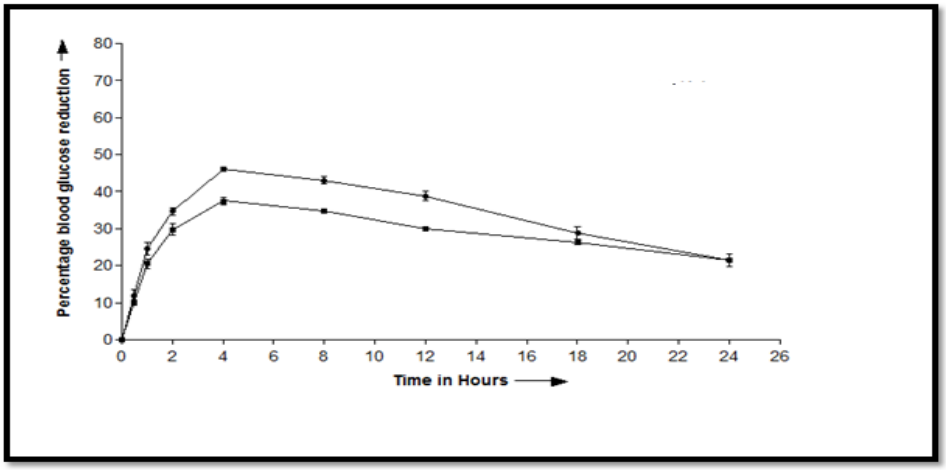

Figure 07: % BGL with pioglitazone before and after itraconazole treatment in diabetic albino rats

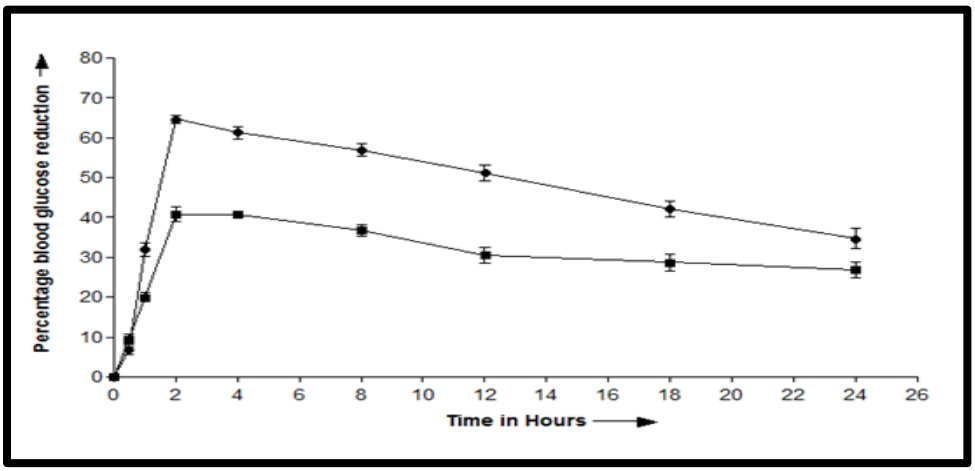

Figure 08: % BGL reduction with repaglinide before and after itraconazole treatment in diabetic albino rats

4. Conclusion

From study it was concluded that hypoglycemia may be observed with pioglitazone and repaglinide after Itraconazole pretreatment at pharmacokinetic level.

References:

[1] Dennis SS, John MN. Case Study: Infections in Diabetes Mellitus. Diabetes Spectrum. 2002; 15 (1): 37-40.

[2] Joshi N, Caputo G, Weitekamp M, Karchmer A: Infections in patients with diabetes mellitus. N Engl J Med. 1999; 341: 1906-12.

[3] Wheat L: Infection and diabetes mellitus. Diabetes Care 1980, 3:187–97.

[4] Maciejewska A, Jaskółowska A, Kwaśniewska J. Fungi in patients with diabetes mellitus type II: prevalence, species of isolated strains. Wiad Parazytol 2004; 50(2):163-70.

[5] Uplanchiwar VP, Hiradeve SM, Fulzele VB, Mansoori MH and Jain H: Influence of lornoxicam on hypoglycemic potential of some oral hypoglycemic agents in normal and diabetic rats. Int J Pharm Sci & Res 2022; 13(1): 302-08. doi: 10.13040/IJPSR.0975-8232.13(1).302-08

[6] Patel, Kaushal, Rajeev Kumar Bheemachari, Vaibhav Uplanchiwar, and Sushil Raut. "Influence of Rimonabant on oral hypoglycemic activity of Glibenclamide and Glipizide on albino & diabetic rat." (2011).

[7] Bheemachari, Setty RS. Influence of Higher Dose of Itraconazole on Sulfonylurea-Induced Hypoglycemia in Albino Rats. The Antiseptic July 2005; 102(7): 376-378.

[8] Setty RS, Bheemachari, Joshi VG, Anand Kumar Y, Pandit J, Venkat Rao N Rambhimaiah

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

S. Influence of Itraconazole on Sulfonylureas-Induced Hypoglycemia in Diabetic Rats. Ind J Pharm Sci 2005; 67 (6): 677-680.

[9] Dhingra P L. Granulomatous Diseases of Nose In: Diseases of Ear, Nose and Throat 3rd ed. Elsevier 2004; p. 197.

[10] Lionel Vincent, François Biron, Philippe Jardin , Marie-Antoinette Piens, Eric Dannaoui, Sylvie Isaac, Benoît Guibert, Yves Pacheco. Pulmonary mucormycosis in a diabetic patient. Ann Med Interne 2000; 151:669-672.

[11] Tapper-Jones LM, Aldred MJ, Walker DM, Hayes TM. Candidal infections and populations of Candida albicans in mouth of diabetics. J Clin Pathol Jul 1981; 34(7): 706-711.

[12] Dorko E, Baranová Z, Jenca A, Kizek P, Pilipcinec E, Tkáciková L. Diabetes mellitus and candidiases. Folia Microbiol (Praha) 2005; 50(3):255-61.

[13] Gupta AK, Konnikov N, MacDonald P, Rich P, Rodger NW, Edmonds MW, McManus R, Summerbell RC: Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. Br J Dermatol 1998; 139: 665–71.

[14] Pierard GE, Pierard-Franchimont C. The nail under fungal siege in patients with type II diabetes mellitus. Mycoses 2005; 48:339–42.

[15] Lugo-Somolinos A, Sanchez JL: Prevalence of dermatophytosis in patients with diabetes. J Am Acad Dermatol 1992; 26:408–10.

[16] Alteras I, Saryt E: Prevalence of pathogenic fungi in the toe-webs and toe-nails of diabetic patients. Mycopathologia 1979; 67:157–59.

[17] Romano C, Massai L, Asta F, Signorini AM:Prevalence of dermatophytic skin and nail infections in diabetic patients. Mycoses 2001; 44:83–6.

[18] Dogra S, Kumar B, Bhansali A, Chakrabarty A. Epidemiology of onychomycosis in patients with diabetes mellitus in India. Int J Dermatol 2002; 41:647–51.

[19] Tapper-Jones LM, Aldred MJ, Walker DM, Hayes TM. Candidal infections and populations of Candida albicans in mouth of diabetics. J Clin Pathol Jul 1981; 34(7): 706-711.

[20] Dorko E, Baranová Z, Jenca A, Kizek P, Pilipcinec E, Tkáciková L. Diabetes mellitus and candidiases. Folia Microbiol (Praha) 2005; 50(3):255-61.

[21] Waugh J, Keating GM, Plosker GL, Easthope S, Robinson DM. Pioglitazone: a review of its use in type II diabetes mellitus. Drugs 2006; 66:85-109.

[22] Wenjiang Z, Yamini R, Tansel K, Helma N, Rachel FT, Edward MS. Inhibition of

[23] cytochrome P450 by antifungal imidazole derivatives. The Ame Soc for Pharmacol and

[24] Exp Ther 2002; 30(3):314-18.

[25] Eckland DA, Danhof M. Clinical pharmacokinetics of pioglitazone. Exp Clin Endocrinol Diabetes. 2000; 108(2):234-42.

[26] Hanefeld M. Pharmacokinetics and clinical efficacy of pioglitazone. Int J Clin Pract. 2001; 121: 19-25.

[27] Kajosaari LI, Jaakkola T, Neuvonen PJ, Backman JT. Pioglitazone, an *in vitro* inhibitor of CYP2C8 and CYP3A4, does not increase the plasma concentrations of the CYP2C8 and CYP3A4 substrate repaglinide. Eur J Clin Pharmacol. 2006 Mar; 62(3):217-23.

[28] Rajendra. Studies on the influence of lansoprazole on the hypoglycaemic activity of glibenclamide and tolbutamide in normal albino rabbits, rats and alloxon induced diabetic rats. M. Pharm dissertation submitted to Rajiv Gandhi University Bangalore. 1999.

[29] Eswar Kumar, K., Ramesh, A., Satyanarayana, S., 2008. Pharmacodynamic and Pharmacokinetic Drug Interaction of Gliclazide and Lacidipine in Animal Models. Indian J. Pharm. Educ. Res. 42 (3), 277-281.

[30] Satyanarayana, S., Prasad, K., Nitin, M., 2003. Pharmacodynamic drug interaction of selegiline and tolbutamide in rats. Indian drugs. 40(6), 366-8.

[31] Trinder, P., 1969. Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor. Ann. Clin. Biochem. 6, 24-7.

[32] Lalchand D. Devhare, A. P. Ghugare, B. P. Hatwar, D. C. Goupale. Method development for determination of water content from various materials by spectrophotometry and it's validation. International journal of drug delivery, 2015, 7(4), 233-240.

[33] Lalchand D. Devhare, P. K. Kore. A Recent Review On Bioavailability And Solubility Enhancement Of Poorly Soluble Drugs By Physical And Chemical Modifications. Research

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

chronicle in health sciences. 2016, 2(5), 299-308.

[34] T. U. Tonde, R. H. Kasliwal, Lalchand D. Devhare. Quantitative estimation of bacoside a in polyherbal memory enhancer syrup for memory boosting activity using hptlc method. Research chronicle in health sciences. 2016, 2(6), 315-320.

[35] A. P. Ghugare, Lalchand D. Devhare, B. P. Hatwar. Development and validation of analytical methods for the simultaneous estimation of Nimorazole and Ofloxacin in tablet dosage form. International journal of drug delivery. 2016,8(3), 96-98.

[36] Harshal. G. Salpe, Lalchand D. Devhare, Anjali Ghugre, & Navjot Singh. Formulation and evaluation of hpmc coated diltiazem hcl tablet and its comparison with other marketed preparation. Research chronicle in health sciences. 2016, 3(1), 11-17.

[37] A. A. Makhani and Lalchand D. Devhare. Development and validation of vierordt's spectrophotometric method for simultaneous estimation of drotaverine and nimesulide combination. Research chronicle in health sciences. 2017, 3(2), 22-28.

[38] A. Makhani and Lalchand D. Devhare. Development and validation of analytical methods for drotaverine and nimesulide combination. Research chronicle in health sciences. 2017, 3(3), 40-44.

[39] Gayatri Katole, Lalchand D Devhare et al. Recent insight into some emerging natural resources with remarkable hepatoprotective potentials. International journal of pharmaceutical science and research. 2020, 5(1),41-47.

[40] Vaibhav P Uplanchiwar, Sushil Yadaorao Raut, Lalchand D Devhare, et al. Pharmacological assessment of antiulcer activity of gloriosa superba linn tubers in experimentally induced gastric ulcers. Journal of medical pharmaceutical and allied science. 2021, 10(3), 2852-2856.

[41] Lalchand D. Devhare and Niharika Gokhale. Acid Neutralizing capacity and antimicrobial potential of selected solvent extract from various indigenous plant. Journal of Advanced Scientific Research (JASR). 2021, 12(4), 175-179.

[42] Lalchand D. Devhare and Niharika Gokhale. Antioxidant and antiulcer property of different solvent extracts of cassia tora linn. Research journal of pharmacy and technology. 2022, 15(3), 1109-1113.

[43] Lalchand D. Devhare and Niharika Gokhale. In silico anti-ulcerative activity evaluation of some bioactive compound from cassia tora and butea monosperma through moleculer docking approach. International journal of pharmaceutical sciences and research. 2023, 14(2), 1000-08.

[44] Lalchand D. Devhare and Niharika Gokhale. A brief review on: phytochemical and antiulcer properties of plants (fabaceae family) used by tribal people of gadchiroli maharashtra. International journal of pharmaceutical sciences and research. 2023, 14(4), 1572-1593

[45] Nikam Nikita R, Akotkar Vaishnavi, Devhare D Lalchand, et al. Parenteral drug delivery approach: an overview. Journal of xidian university. 2023, 17(1), 386-400.

[46] Shubham M. Shende , Pooja Bhandare, Lalchand D Devhare, et al. In-vitro: micropropagation of mint and investigate the antibacterial activity of mint extract. Eur. Chem. Bull. 2023, 12(Special Issue 5), 780 – 784

[47] Shishupal S. Bodhankar, Lalchand D.Devhare, et al. Formulation and in vitro evaluation of dental gel containing ethanglic extract of Mimosa Pudica. Eur. Chem. Bull. 2023, 12(5), 1293-1299

[48] Lalchand D. Devhare, Shishupal S. Bodhankar, et al. Important role of food and nutritional security during Covid-19: A survey. Eur. Chem. Bull. 2023, 12(5), 1363-1374

[49] Neha R. Pathak, Lalchand D. Devhare, et al. Aclinial reveiew on pharmacological evaluation of Thiazolidine and Isatin in the new millenium as magic moieties. Eur. Chem. Bull. 2023, 12(5), 3410-3417.

[50] Shailja Singh, Kimee Hiuna Minj, Lalchand D Devhare, et al. An update on morphology, mechanism, lethality, and management of dhatura poisoning. Eur. Chem. Bull. 2023, 12(5), 3418-3426.

[51] Pravin B. Suruse, B. A. Jadhav, Lokesh G. Barde, Lalchand D Devhare et al. Exploring the potential of Aerva Lanata extract in a herbal ointment for fungal infection treatment. Journal of Survey in Fisheries Sciences.10(1), 1922-1932

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[52] Shubham Shende, Bhagyashri Meshram, Heera Karemore, Lalchand D Devhare. et al. Development And Characterization of Glycerogelatin Suppositories For Enhanced Efficacy. European Journal of Pharmaceutical and Medical Research. 2023, 10(6), 522-528

[53] Vinod M. Thakare, Shraddha A. Umare, Lalchand D Devhare et al. Separation and purification of carboxymethyl cellulose from Spinacia Oleracea for use in pharmaceutical dosage form. Eur. Chem. Bull. 2023, 12(5), 4062-4080.

[54] Pravin B. Suruse, Aakansha P. Deshmukh, Lokesh G. Barde, Lalchand D Devhare et al. Rimegepant-embedded fast dissolving films: A novel approach for enhanced migraine relief. Journal of Survey in Fisheries Sciences. 10(1), 2071-2084

[55] Mahesh Prasad, Abhishek Suman, Swati Srivastava, Lalchand D Devhare et al. Butea monosperma stem bark extract partially reverses high fat diet-induced obesity in rats. Eur. Chem. Bull. 2023, 12(Reg Issue 5), 4267 – 4273.

[56] Sushil Raut, Vaibhav Uplanchiwar, Avinash Gahane, Santosh Bhadoriya, Shrishail Patil, Sunil K Jain. Development, characterization and investigation of anti-inflammatory potential of valdecoxib topical gels. 2012, NISCAIR-CSIR, India