A Bird's Eye View on Pharmacotherapeutic Progress of Indolizine-based Compounds in Context to Modern Scenario

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ABSTRACT

Introduction: Indolizine (INDO) is a bicyclic heteroaromatic compound containing two fused rings (10 pi-electron system); pyridine and pyrrole via bridging N-atom at the centre of both the rings. This scaffold exists very rarely in nature and is an isomeric form of indole. It is analogous of indole (isoelectrically resembles indole system) which has marked potency in the biological activity. The scaffold is also related to the heterocyclic compound purine which is the base of cellular organisms. The structure of INDO is found in many natural products and is important in the pharmaceutical area because of prominent biological properties.

Aims: Highlighting the recent pharmacotherapeutic progress of indolizine-based compounds.

Methodology: In the preparation of this review article, a comprehensive scrutiny of the published literature in diverse pharmaceutical and medical databases such as Google Scholar, PubMed, etc. was successfully conducted and classified accordingly.

Results: The derivatives of INDO have various applications in drug design, biological area, and pharmaceutical research. INDO is a pharmacological active moiety and broadly displays biological activities such as anti-microbial, hypoglycemic, anti-inflammatory, analgesic, anti-oxidant, anti-depressant, anti-cancer activities, etc. The substituents on the INDO nucleus ring exhibit a wide range of biological activities such as anti-cancer, anti-bacterial, anti-fungal, anti-tubercular, anti-histamine, CNS-depressant activity, etc.

Conclusion: This imperative review article broadly highlighted the summary of the diverse pharmacotherapeutic potentials of INDO. This review will be a true inspiration for the medicinal chemists and pharmacologists in designing and screening low-molecular-weight inhibitors of the INDO scaffold.

Key Words: Indolizine, Derivatives, Pharmacology, Therapeutics, Targets, Inhibitors

INTRODUCTION

Indolizine (INDO) is a bicyclic heteroaromatic compound containing two fused rings (10 pi-electron system); pyridine and pyrrole via bridging N-atom at the centre of both the rings (Figure 1). This scaffold exists very rarely in nature and is an isomeric form of indole.¹ It is analogous of indole (isoelectrically resembles indole system) which has marked potency in the biological activity.² The scaffold is also related to the heterocyclic compound purine which is the base of cellular organisms.³ In this structure, various modifications, observations, and investigations have been reported over time.

Figure 1: Structure of Indolizine.

INDO is a pharmacological active moiety and broadly displays biological activities such as anti-microbial⁴, hypoglycemic⁵, anti-inflammatory⁶, analgesic⁷, anti-oxidant⁸, anti-depressant⁹, anti-cancer activities (Figure 2).^{10,11} The structure of the INDO is found in many natural products and

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is important in the pharmaceutical area because of prominent biological properties.¹² The derivatives of INDO have various applications in drug design, biological area, and pharmaceutical research.¹³ Recently, the derivatization of INDO has been a core area of research due to the presence of the heterocyclic structure in several alkaloids extracted from neotropical frogs.^{14,15} Although, some methods have been published such as the racemic form of INDO derivatives, yet limited literature of enantiomeric selective has been reported.^{16,17}

Figure 2: Biological activities of Indolizine.

PHARMACOLOGICAL ACTIVITIES

The substituents on INDO nucleus ring exhibit a wide range of biological activities such as anti-cancer¹⁸, anti-bacterial¹⁹, anti-fungal²⁰, anti-tubercular²¹, anti-histamine²², CNS-depressant activity²³, etc.

Anti-tubercular activity

Tuberculosis is one of the dangerous respiratory diseases caused preliminary by *Mycobacterial tuberculosis* and is one of the primary reasons for both disability and death.²⁴ According to the World Health Organization (WHO), more than 95% of people death is reported in a low and middle-income country. In addition to it, 0.4 million people expired from tuberculosis who are suffering from HIV infections.²⁵ From the data, it was evidenced that more than 500 thousand people developed resistance against multi-drug and rifampicin drug therapy which required the need for the new anti-TB drugs with better pharmacokinetic attributes.²⁶ INDO derivatives have been evaluated through *in vitro* assay for anti-TB properties against H37Rv and multidrug resistance strain.^{27,28} Gundersen et al. synthesized a series of 1-substituted INDO analogues and screened for the mycobacterial inhibitory activity where these compounds demonstrated effective minimum inhibitory activity (MIC, it is the minimal concentration at which the drug substance demonstrates no noticeable microbial growth over the Petri dish) at concentration 6.25 µg/mL.²⁹

Anti-microbial activity

Srikanth et al. synthesized a series of 1-carbohydrazone INDO derivatives and screened against *Staphylococcus aureus*, *Escherichia coli*, and *P. aeruginosa*.³⁰ The anti-bacterial activity (*Bacillus subtilis*, *S. aureus*, *S. faecalis*, *M. luteus*, and *E. coli*) of the new series of carbonitrile INDO derivative was screened by Hazra et al.³¹

Anti-fungal activity

The frequency of fungal diseases has augmented significantly in the past 50 years. Fungal diseases have marked themselves differently including mycoses in the skin, hair, nails, but also as systemic mycoses.³² The last reason, systemic mycoses, remains the major medical issue due to amplification in the immunocompromised patient population. One of the most common fungal infections is candidiasis, caused primarily by *Candida albicans*, a diploid fungus that grows both as yeast and filamentous cells.³³ This fungus can also inflate resistance to anti-mycotic drugs that already subsist in the market, which necessitates a constant search for new drugs and treatments.³⁴ A newly synthesized series of 3-substituted INDO-1-carbonitrile derivatives have been screened for their antifungal activity and recently been recognized as phosphatase inhibitor.^{35,36}

Anti-cancer activity

Cancer is constantly rising health risk and mortality rate.³⁷ About, 25% of patients show a familial history of the disease which causes responsible factors like genes and environment.^{38,39} INDO nucleus has been reported to exhibit potential anti-cancer activity. Recently, novel heterocyclic indozolyl glyoxylamide derivatives have been synthesized and screened against MDR cell lines of cancer where these compounds were found to be active.^{40,41} The researchers have reported derivatives which were effective as anti-cancer through the destabilization of microtubules in the cancer cell. The researchers also studied that these derivatives presented marked effectiveness against multidrug resistance (MDR) cell lines without any neurotoxicity.⁴²

Anti-histamine and Central Nervous System (CNS) depressant activities

Histamine exhibits allergic and hypersensitivity reactions by the action of antigen and antibodies.⁴³ Depression is referred to an imbalance between neurotransmitters which leads to psychosis and ultimately death. Approximately, 5% of the worldwide populations are suffered from these conditions which emerged the development of newer drug therapy.⁴⁴ Recently, synthesized alkyl INDO derivatives have been reported which expressed both anti-depressant and anti-histaminic activities.⁴⁵⁻⁴⁷

Cellular Apoptosis

INDO is present in various natural products such as homocrepidine-A⁴⁸, tashiromine⁴⁹, swainsonine⁵⁰, Pandalisines-A and Pandalisines-B⁵¹, Flueggidine⁵², etc. which expresses multifarious biological activities such as anti-herpes virus⁵³, cyclooxygenase and lipoxygenase inhibitors⁵⁴, anti-tuberculosis⁵⁵, and acetylcholine receptor agonist.⁵⁶ p53, a well-known component in apoptosis-inducer and tumor suppressor has been a bird's eye for modern-day researchers.⁵⁷⁻⁵⁸ A recent study indicated that the tumor suppressor (p53) in the C3 cell induces apoptosis with different genotypic profiles like p53HepG2, p53 null Hep3B, and mutant p53 Huh-7.⁵⁹ It was initiated that C3 presented a marked anti-proliferation of HepG2 cells as compared with other cell lines and activation of p53 is related with the amplification of ROS production.^{60,61} It was found that carboxylated derivatives of INDO have been markedly effective towards the induction of apoptosis through the mitochondria p53 pathway in HepG2 cell.⁶²⁻⁶⁶

Anti-angiogenesis effect

During the last decades, the investigation was carried out for decorated polyfunctional scaffold with fluorescent INDO derivatives bearing various orthogonal groups such as amines, esters, oximes, alkynes, etc. with the anti-angiogenic drug COB223 (ERK1/2 inhibitor) that was structurally similar to the INDO scaffold. This scaffold showed binding with the ribonucleic acid (RNA) protein which effectively inhibited the process of angiogenesis.⁶⁷⁻⁶⁸

CONCLUSION

This imperative review article broadly highlighted the summary of the diverse pharmacotherapeutic potentials (hypoglycemic, anti-inflammatory, analgesic, anti-oxidant, anti-depressant, anti-cancer, anti-bacterial, anti-fungal, anti-tubercular, anti-histamine, etc.) of numerous Indolizine derivatives. This interesting reviewed literature content will be a true inspiration for the modern-day medicinal chemists and motivated pharmacologists in rationally designing and *in vivo* / *in vitro* screening of low-molecular-weight inhibitors bearing Indolizine scaffold. The comprehensive study opened new avenues of research and application perspectives in identifying the potential leads.

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Conflict of Interest

Authors declare no conflict of interest regarding the publication of this article.

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Authors' Contribution

KRD: Physically authored the whole manuscript

PK: Complete literature survey performed

DKM: Made Figures, Wrote Structured Abstract, Drawn Graphical Abstract, Set References

UNM: Final reviewing of this manuscript, provided suggestions, and corrected few errors

REFERENCES

- William HB, Doerge RF. Mannich bases from 2-Phenyl Indolizine-II. *J Pharm Sci* 1967;56(9):1200-2.
- Gupta RR, Kumar M, Gupta V. Benzo-Fused Five-Membered Heterocycles with One Heteroatom. In: *Heterocyclic Chemistry*. Berlin: Springer; 1999.
- Belal A, Gouda AM, Ahmed AS, Gawad NM. Synthesis of novel INDO, diazepino Indolizine and Pyrimido Indolizine derivatives as potent and selective anticancer agents. *Res Chem Intermed* 2015;41(12):9687-701.
- Gundersen LL, Negussie AH, Rise F, Oestby OB. Antimycobacterial Activity of 1-Substituted Indolizine. *Arch Pharm* 2003;336(3):191-5.
- De AU, Saha BP. Indolizines II: search for potential oral hypoglycemic agents. *J Pharm Sci* 1975;64(2):249-52.
- Kallay KR, Doerge RF. p-Substituted 1, 2-diphenyl Indolizine as anti-inflammatory agents. *J Pharm Sci* 1972;61(6):949-51.
- Som S, Das AK. Synthesis and evaluation of some 3-benzoyl Indolizine-1-carboxamides as possible anti-inflammatory and analgesic agents. *Oriental J Chem* 2006;22(2):415-20.
- Østby OB, Dalhus B, Gundersen LL, Rise F, Bast A, Haenen GR. Synthesis of 1-Substituted 7-Cyano-2, 3-diphenyl Indolizines and Evaluation of Antioxidant Properties. *Eur J Org Chem* 2000;2000(22):3763-70.
- Siddiqui N, Andalip SB, Ali R, Afzal O, Akhtar MJ, Azad B, et al. Antidepressant potential of nitrogen-containing heterocyclic moieties: an updated review. *J Pharm Bioallied Sci*. 2011;3(2):194-212.
- Olejnikova P, Bírošová L, Švorc L. Antimicrobial and antimutagenic properties of newly synthesized derivatives of Indolizine. *Sci Pharm* 2009;77(7):216.
- Wani MC, Nicholas AW, Wall ME. Plant antitumor agents. 28. Resolution of a key tricyclic synthon, 5'(RS)-1, 5-dioxo-5'-hydroxy-2'H, 5'H, 6'H-6'-oxopyrano [3', 4'-f]. delta. 6, 8-tetrahydro Indolizine: total synthesis and antitumor activity of 20 (S)- and 20 (R)-camptothecin. *J Med Chem* 1987;30(12):2317-9.
- Venugopala KN, Khedr MA, Attimarad M, Padmashali B, Kulkarni RS, Venugopala R, et al. Review on chemistry of natural and synthetic Indolizines with their chemical and pharmacological properties. *J Basic Clin Pharm* 2017;8(2):51-9.
- Flitsch W. In: *Comprehensive Heterocyclic Chemistry*. Katritzky AR; Rees CW, Eds. Oxford: Pergamon Press; 1984.
- Daly JW, Spande TF, Garraffo HM. Alkaloids from amphibian skin: a tabulation of over eight-hundred compounds. *J Nat Prod* 2005;68(10):1556-75.
- Daly JW, Spande TF. *Alkaloids Chemical and Biological Perspectives*. New York: Wiley Science; 1986.

16. Elattar KM, Youssef I, Fadda AA. Reactivity of Indolizines in organic synthesis. *Synth Commun* 2016;46(9):719-44.
17. Occhiato EG, Guarna A, Spinetti LM. Enantioselective synthesis of Indolizine derivatives by rearrangement-cyclization of isoxazoline-5-spirocyclopropanes. *Tetrahedron* 1993;49(46):10629-42.
18. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127(12):2893-917.
19. Gundersen LL, Negussie AH, Rise F, Oestby OB. Antimycobacterial Activity of 1-Substituted Indolizines. *Arch Pharm* 2003;336(3):191-5.
20. Faghih-Mirzaei E, Seifi M, Abaszadeh M, Zomorodian K, Helali H. Design, synthesis, biological evaluation and molecular modeling study of novel Indolizine-1-carbonitrile derivatives as potential anti-microbial agents. *Iranian J Pharm Res* 2018;17(3):883-95.
21. Dye C, Williams BG. The population dynamics and control of tuberculosis. *Science*. 2010;328(5980):856-61.
22. Jose B, Fake CS, Joine KF, Miner WD. 5HT₃ receptor antagonists, indazole and INDO-3 carboxylic acid derivatives. *J Med Chem* 1987;30:2317-9.
23. Ippolito A, Claudi F, Gulini U, Micossi L. Indolizine derivatives with biological activity for 3-(2-aminoethyl)-2-methylINDO and their N-alkyl derivatives. *J Pharm Sci* 1979;68:321-4.
24. Ma Z, Lienhardt C, McIlerron H, Nunn AJ, Wang X. Global tuberculosis drug development pipeline: the need and the reality. *Lancet* 2010;375(9731):2100-9.
25. Crabb C. Global Alliance at full steam for new TB drugs. *Bull World Health Org* 2002;80:517.
26. Johnson TO, Ermolieff J, Jirousek MR. Protein tyrosine phosphatase 1B inhibitors for diabetes. *Nature Rev Drug Discov* 2002;1(9):696-709.
27. Dulla B, Wan B, Franzblau SG, Kapavarapu R, Reiser O, Iqbal J, et al. Construction and functionalization of fused pyridine ring leading to novel compounds as potential antitubercular agents. *Bioorg Med Chem Lett* 2012;22(14):4629-35.
28. Moraski GC, Markley LD, Chang M, Cho S, Franzblau SG, Hwang CH, et al. Generation and exploration of new classes of antitubercular agents: the optimization of oxazolines, oxazoles, thiazolines, thiazoles to imidazo [1, 2-a] pyridines and isomeric 5, 6-fused scaffolds. *Bioorg Med Chem* 2012;20(7):2214-20.
29. Gundersen LL, Charnock C, Negussie AH, Rise F, Teklu S. Synthesis of Indolizine derivatives with selective antibacterial activity against *Mycobacterium tuberculosis*. *Eur J Pharm Sci* 2007;30(1):26-35.
30. Lingala S, Nerella R, Cherukupally R, Das AK. Synthesis and comparative antitubercular activity of INDO derivatives of isoniazid/pyrazinamide/ethionamide. *Int J Pharm Sci Rev Res*. 2011;6:128-31.
31. Hazra A, Mondal S, Maity A, Naskar S, Saha P, Paira R, et al. Amberlite-IRA-402 (OH) ion exchange resin mediated synthesis of INDOs, pyrrolo [1, 2-a] quinolines and isoquinolines: Antibacterial and antifungal evaluation of the products. *Eur J Med Chem* 2011;46(6):2132-40.
32. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. *J Fungi* 2017;3(4):57.
33. Kabir MA, Hussain MA, Ahmad Z. *Candida albicans*: a model organism for studying fungal pathogens. *ISRN Microbiol* 2012;2012:538694.
34. Sangamwar AT, Deshpande UD, Pekamwar SS. Antifungals: need to search for a new molecular target. *Ind J Pharm Sci* 2008;70(4):423-30.
35. Weide T, Arve L, Prinz H, Waldmann H, Kessler H. 3-Substituted Indolizine-1-carbonitrile derivatives as phosphatase inhibitors. *Bioorg Med Chem Lett* 2006;16(1):59-63.
36. Lemke TL. Antiparasitic agents. In: Williams, D.A., Lemke, T.L. (Eds.), *Foye's Principles of Medicinal Chemistry*. Philadelphia: Lipincott Williams and Wilkins; 2002.
37. James DA, Koya K, Li H, Liang G, Xia Z, Ying W, et al. Indole- and Indolizine-glyoxylamides displaying cytotoxicity against multidrug resistant cancer cell lines. *Bioorg Med Chem Lett*. 2008;18(6):1784-7.
38. Haydon AM, Jass JR. Emerging pathways in colorectal-cancer development. *Lancet Oncol* 2002;3(2):83-8.
39. Cingolani GM, Claudi F, Venturi F. INDO derivatives with biological activity V. 1-(2-Aminoethyl)-2-methyl Indolizine and its N-alkyl derivatives. *Eur J Med Chem* 1988;23(3):291-4.
40. Guggilapu SD, Lalita G, Reddy TS, Prajapati SK, Nagarsenkar A, Ramu S, et al. Synthesis of C5-tethered indolyl-3-glyoxylamide derivatives as tubulin polymerization inhibitors. *Eur J Med Chem*. 2017;128:1-12.
41. Danko B, Martins A, Chuang DW, Wang HC, Amaral L, Molnár J, et al. In vitro cytotoxic activity of novel protoflavone analogs-selectivity towards a multidrug resistant cancer cell line. *Anticancer Res*. 2012;32(7):2863-9.
42. Kapoor S, Srivastava S, Panda D. Indibulin dampens microtubule dynamics and produces synergistic antiproliferative effect with vinblastine in MCF-7 cells: Implications in cancer chemotherapy. *Sci Rep* 2018;8(1):12363.
43. Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nature Med* 2012;18(5):693-704.
44. Leo J, Lacasse JR. The media and the chemical imbalance theory of depression. *Soc* 2008;45(1):35-45.
45. Morita K, Yamamoto, Iwata H. Synthesis of INDO derivatives, *Biochem Pharmacol* 1973;22:111-5.
46. Kerzare DR, Menghani SS, Khedekar PB. Synthesis, characterization, antidepressant activity and docking studies of some novel indole bearing azetidinone derivatives. *Drugs* 2018;52(1):110-21.
47. Siddiqui N, Andalip SB, Ali R, Afzal O, Akhtar MJ, Azad B, et al. Antidepressant potential of nitrogen-containing heterocyclic moieties: an updated review. *J Pharm Bioallied Sci* 2011;3(2):194-212.
48. Hu Y, Zhang C, Zhao X, Wang Y, Feng D, Zhang M, et al. (±)-Homocrepidine A, a pair of anti-inflammatory enantiomeric octahydro Indolizine alkaloid dimers from *Dendrobium crepidatum*. *J Nat Prod* 2016 22;79(1):252-6.
49. Marsden SP, McElhinney AD. Total synthesis of the indolizidine alkaloid tashiromine. *Beilstein J Org Chem* 2008;4(1):8.
50. Lee BK, Choi HG, Roh EJ, Lee WK, Sim T. Stereoselective synthesis of (–)-8-epi-swainsonine starting with a chiral aziridine. *Tetrahedron Lett* 2013 6;54(6):553-6.
51. Cheng YB, Tsai YH, Lo IW, Huang CC, Tsai YC, Beerhues L, et al. Pandalisines A and B, novel indolizidine alkaloids from the leaves of *Pandanus utilis*. *Bioorg Med Chem Lett*. 2015;25(19):4333-6.
52. Zhao BX, Wang Y, Li C, Wang GC, Huang XJ, Fan CL, et al. Flueggidine, a novel axisymmetric indolizidine alkaloid dimer from *Flueggea virosa*. *Tetrahedron Lett* 2013;54(35):4708-11.
53. De Bolle L, Andrei G, Snoeck R, Zhang Y, Van Lommel A, Otto M, et al. Potent, selective and cell-mediated inhibition of human herpesvirus 6 at an early stage of viral replication by the non-nucleoside compound CMV423. *Biochem Pharmacol* 2004;67(2):325-36.
54. Shrivastava SK, Srivastava P, Bandresh R, Tripathi PN, Tripathi A. Design, synthesis, and biological evaluation of some novel

- Indolizine derivatives as dual cyclooxygenase and lipoxygenase inhibitor for anti-inflammatory activity. *Bioorg Med Chem* 2017;25(16):4424-32.
55. Gundersen LL, Charnock C, Negussie AH, Rise F, Teklu S. Synthesis of Indolizine derivatives with selective antibacterial activity against *Mycobacterium tuberculosis*. *Eur J Pharm Sci* 2007;30(1):26-35.
56. Xue Y, Tang J, Ma X, Li Q, Xie B, Hao Y, et al. Synthesis and biological activities of INDO derivatives as α -7 nAChR agonists. *Eur J Med Chem* 2016;115:94-108.
57. Wickramasekera NT, Das GM. Tumour suppressor p53 and estrogen receptors in nuclear-mitochondrial communication. *Mitochondrion* 2014;16:26-37.
58. Wang K. Molecular mechanisms of hepatic apoptosis regulated by nuclear factors. *Cellular Signal* 2015;27(4):729-38.
59. Müller M, Strand S, Hug H, Heinemann EM, Walczak H, Hofmann WJ, et al. Drug-induced apoptosis in hepatoma cells is mediated by the CD95 (APO-1/Fas) receptor/ligand system and involves the activation of wild-type p53. *J Clin Invest* 1997;99(3):403-13.
60. Yin M, Ren X, Zhang X, Luo Y, Wang G, Huang K, et al. Selective killing of lung cancer cells by miRNA-506 molecule through inhibiting NF- κ B p65 to evoke reactive oxygen species generation and p53 activation. *Oncogene* 2015;34(6):691-703.
61. Chen P, Luo X, Nie P, Wu B, Xu W, Shi X, et al. CQ synergistically sensitizes human colorectal cancer cells to SN-38/CPT-11 through lysosomal and mitochondrial apoptotic pathway via p53-ROS cross-talk. *Free Radical Biol Med* 2017;104:280-97.
62. Li W, Laskar A, Sultana N, Osman E, Ghosh M, Li Q, et al. Cell death induced by 7-oxysterols via lysosomal and mitochondrial pathways is p53-dependent. *Free Radical Biol Med* 2012;53(11):2054-61.
63. Zhou Y, Wei L, Zhang H, Dai Q, Li Z, Yu B, et al. FV-429 induced apoptosis through ROS-mediated ERK2 nuclear translocation and p53 activation in gastric cancer cells. *J Cell Biochem* 2015;116(8):1624-37.
64. Tu W, Zhang Q, Liu Y, Han L, Wang Q, Chen P, et al. Fluoride induces apoptosis via inhibiting SIRT1 activity to activate mitochondrial p53 pathway in human neuroblastoma SH-SY5Y cells. *Toxicol Appl Pharmacol* 2018;347:60-9.
65. Dashzeveg N, Yoshida K. Cell death decision by p53 via control of the mitochondrial membrane. *Cancer Lett* 2015;367(2):108-12.
66. Kruiswijk F, Labuschagne CF, Vousden KH. p53 in survival, death and metabolic health: a lifeguard with a licence to kill. *Nature Rev Mol Cell Biol* 2015;16(7):393-405.
67. Vanek V, Picha J, Fabre B, Budesinsky M, Lepsik M, Jiracek J. The development of a versatile trifunctional scaffold for biological applications. *Eur J Org Chem* 2015;2015:3689-701.
68. Engelen M, Lombardi A, Vitale R, Lista L, Maglio O, Pavone V, Nastri F. Branched porphyrins as functional scaffolds for multisite bioconjugation. *Biotechnol Appl Biochem* 2015;62(3):383-92.