BEMS Reports. 2022; 8(2): 24-27.
A Multifaceted Peer Reviewed Journal in the field of Biology, Medicine, Engineering and Science
www.bemsreports.org | www.phcog.net

Research Article

Pharmacological Targets of Asundexian Relevant to its Therapeutic Efficacy in Treating Cardiovascular Diseases

Arun HS Kumar

ABSTRACT

Background: Oral anticoagulant which don't interfere with haemostasis physiology have potential application in management of acute cardiovascular events. Asundexian is once such oral anticoagulant, which is reported to be beneficial by minimising the rate of ischemic events. This study examined the pharmacological basis for cardiovascular benefits of asundexian. **Materials and Methods:** All potential targets of asundexian in humans were identified by *in silco* screening in the Swiss Target Prediction server and analysed. **Results:** Unexpectedly factor XI or XIa was not observed to be targeted by Asundexian in this study. However factor XII and thrombin were observed to be targeted by Asundexian. In addition several GPCR's, ion channels, enzymes and kinases relevant to positive modulation of cardiovascular physiology were observed to be targeted by Asundexian. **Conclusion:** The anticoagulant effects of asundexian is likely to be by indirect inhibition of factor XI or XIa by interfering with factor XII and/or thrombin. The cardiovascular benefits of asundexian is likely mediated by broader relevant off target effects.

Keywords: Cardiovascular, Myocardial infarction, Thrombosis, Clot, Anticoagulant.

INTRODUCTION

Several studies have reported the feasibility of achieving antithrombotic effects without interfering with the haemostasis physiology by inhibiting factor XI or XIa.[1-3] Currently two orally bioavailable factor XIa inhibitors are being evaluated in various clinical trials for potential use in cardiovascular diseases. Asundexian (BAY-2433334) is reported to be a selective and reversible factor XIa inhibitor which when used together with aspirin and P2Y12 inhibitor was recently reported to be well tolerated among patients with recent acute myocardial infarction.[4] In this study asundexian was reported to dose dependently inhibit factor XIa and as anticipated did not cause any significant increase in bleeding. In addition the incidence of any adverse ischemic events were low among patients receiving asundexian.[4] Although asundexian is reported to selectively inhibit human factor XIa with high potency (IC_{50} of 1 nM),[3] it is likely that other off targets may potentially be involved in its cardiovascular benefits. To evaluate the potential off targets of asundexian, this study looked at the *in silico* approach to identify all possible targets asundexian can interact with in humans.

MATERIALS AND METHODS

The Isomeric SMILES sequence of asundexian retrieved from PubChem database was inputted into the Swiss Target Prediction server to identify all its potential targets as reported before.[5,6]

The network proteins of human factor XIa were screened in the String database as previously described for other proteins.[5,6]

RESULTS

Asundexian was observed to bind to 15 different categories of targets (Figure 1) incidentally all with low but similar probabilities (0.075). The top 25 targets of asundexian were from the following six categories i.e., kinases (40%), phosphodiesterase's (16%), proteases (12%), ion channels (12%), enzymes (12%) and family A GPCR's (8%) (Figure 1). The individual targets from each of these categories are listed in Tables 1 to 7. In this analysis neither factor XI or factor XIa were identified as a target of asundexian.

The network proteins of factor XI were identified from the String data base (Figure 2) and among these networks of factor XI, Thrombin (F2) was identified as a target of asundexian in our screening. Besides Thrombin, four other coagulation related factors were also identified as relevant targets of asundexian (Table 7). An array of GPCR's were also identified as targets of asundexian, which highlights its potential cardiovascular benefits. Among these the prominent targets were adenosine, bradykinin, chemokine and dopamine receptors (Table 6).

Among the kinases targeted by asundexian, macrophage colony stimulating factor receptor,

Cite this article : Kumar AHS. Pharmacological Targets of Asundexian Relevant to its Therapeutic Efficacy in Treating Cardiovascular Diseases. BEMS Reports. 2022;8(2):24-7.

Arun HS Kumar

Stemcology, School of Veterinary Medicine, University College Dublin, Belfield, Dublin, IRELAND.

Correspondence

Dr. Arun HS Kumar, DVM, PhD

School of Veterinary Medicine, University College Dublin, Belfield, Dublin-04, IRELAND.

Email id: arun.kumar@ucd.ie

History

- Submission Date: 03-10-2022;
- Review completed: 25-10-2022;
- Accepted Date: 28-10-2022.

DOI : 10.5530/bems.8.2.6

Article Available online
http://www.bemsreports.org

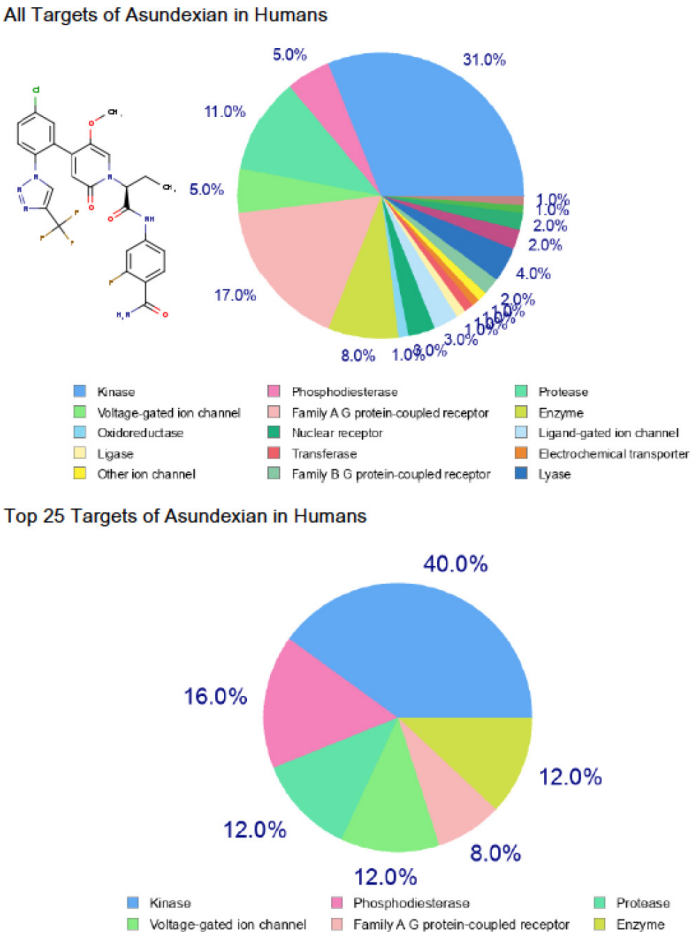

Figure 1: All targets in humans (Top pie chart) of asundexian identified in the Insilco screening. Inset is the chemical structure of asundexian. The selected top 25 targets of asundexian (bottom pie chart).

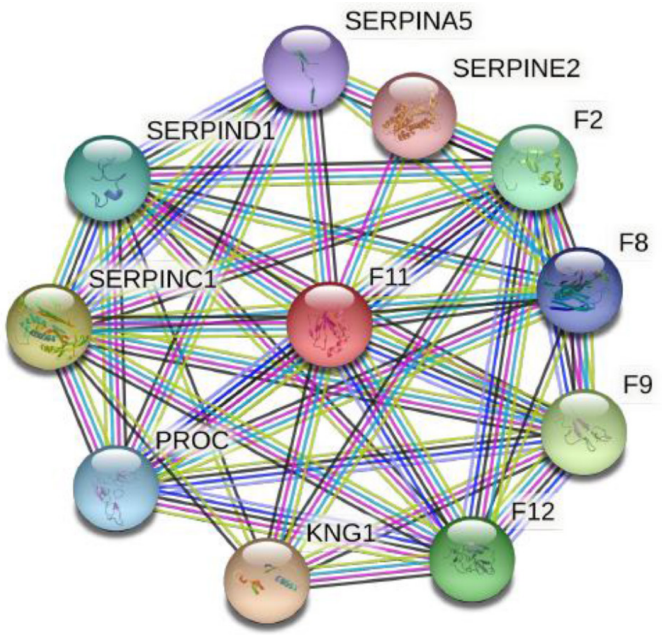

Figure 2: Network proteins of factor XI in humans analysed from the string database.

Table 1: List of Kinases targeted by asundexian.

Target	Uniport ID
Macrophage colony stimulating factor receptor	P07333
Nerve growth factor receptor Trk-A	P04629
Neurotrophic tyrosine kinase receptor type 2	Q16620
Serine/threonine-protein kinase Aurora-A	O14965
Serine/threonine-protein kinase PLK1	P53350
Serine/threonine-protein kinase PLK3	Q9H4B4
Ribosomal protein S6 kinase 1	P23443
MAP kinase ERK2	P28482
Serine/threonine-protein kinase AKT	P31749
Serine/threonine-protein kinase Aurora-B	Q96GD4
c-Jun N-terminal kinase 1	P45983
Tyrosine-protein kinase JAK3	P52333
Tyrosine-protein kinase JAK1	P23458
Tyrosine-protein kinase JAK2	O60674
Leucine-rich repeat serine/threonine-protein kinase 2	Q5S007
Tyrosine-protein kinase BTK	Q06187
Ephrin receptor	P54760
Tyrosine-protein kinase SYK	P43405
Focal adhesion kinase 1	Q05397
Receptor protein-tyrosine kinase erbB-2	P04626
Insulin-like growth factor I receptor	P08069
Rho-associated protein kinase 1	Q13464
c-Jun N-terminal kinase 2	P45984
Inhibitor of nuclear factor kappa B kinase beta subunit	O14920
Glycogen synthase kinase-3 beta	P49841
Fibroblast growth factor receptor 3	P22607
CDK2/Cyclin A	P20248 P24941
Dual specificity mitogen-activated protein kinase kinase 1	Q02750
Serine/threonine-protein kinase Chk1	O14757
Discoidin domain-containing receptor 2	Q16832
Pyruvate dehydrogenase kinase isoform 1	Q15118

Table 2: List of phosphodiesterases targeted by asundexian.

Target	Uniport ID
Phosphodiesterase 5A	O76074
Phosphodiesterase 10A	Q9Y233
Phosphodiesterase 3	Q14432
Phosphodiesterase 4B	Q07343
Phosphodiesterase 2A	O00408

nerve growth factor receptor, insulin-like growth factor I receptor, Rho-associated protein kinase and fibroblast growth factor receptor may have a relevant role in its cardiovascular benefits. The enzyme and ion channel targets of asundexian were of particular interest in modulating cardiovascular physiology (Table 4 and 5).

Table 3: List of proteases targeted by asundexian.

Target	Uniport ID
Complement factor D	P00746
Leukocyte elastase	P08246
Thrombin	P00734
Cathepsin K	P43235
Matrix metalloproteinase 13	P45452
Thrombin and coagulation factor X	P00742
Legumain	Q99538
Cathepsin G	P08311
Cathepsin L	P07711
Cathepsin (B and K)	P07858
Cathepsin S	P25774

Table 4: List of ion channels targeted by asundexian.

Target	Uniport ID
Cholesteryl ester transfer protein	P11597
Sodium channel protein type V alpha subunit	Q14524
Sodium channel protein type IX alpha subunit	Q15858
Vanilloid receptor	Q8NER1
Voltage-gated potassium channel subunit Kv1.5	P22460
Sodium channel protein type X alpha subunit	Q9Y5Y9
Glutamate NMDA receptor; GRIN1/GRIN2A	Q12879 Q05586
Glutamate receptor ionotropic, AMPA 2	P42262
P2X purinoceptor 7	Q99572
Sodium/glucose cotransporter 1	P13866

Table 5: List of enzymes targeted by asundexian.

Target	Uniport ID
PI3-kinase p110-delta subunit	O00329
PI3-kinase p110-alpha subunit	P42336
Acyl-CoA desaturase	O00767
iNOS	P35228
Probable protein-cysteine N-palmitoyltransferase porcupine	Q9H237
Poly [ADP-ribose] polymerase-1	P09874
Diacylglycerol O-acyltransferase 1	O75907
Hepatic lipase	P11150

Table 6: List of Family A G protein-coupled receptors targeted by asundexian.

Target	Uniport ID
Cannabinoid receptor 1	P21554
Cannabinoid receptor 2	P34972
C-C chemokine receptor type 1	P32246
C-C chemokine receptor type 2	P41597
C-X-C chemokine receptor type 3	P49682
Orexin receptor 2	O43614
Orexin receptor 1	O43613
Adenosine A1 receptor	P30542
Adenosine A2b receptor	P29275
Bradykinin B1 receptor	P46663
Bradykinin B2 receptor	P30411
Prolactin-releasing peptide receptor	P49683
Oxytocin receptor	P30559
Interleukin-8 receptor B	P25025
Probable G-protein coupled receptor 52	Q9Y2T5
Dopamine D3 receptor	P35462
Dopamine D2 receptor	P14416
Calcitonin gene-related peptide type 1 receptor	Q16602
Glucagon receptor	P47871

Table 7: List of coagulations factors targeted by asundexian.

Target	Uniport ID
Complement factor D	P00746
Thrombin	P00734
Thrombin and coagulation factor X	P00742
Platelet-derived growth factor subunit B	P01127
Platelet-derived growth factor subunit A	P04085

DISCUSSION

In this study all potential targets of asundexian in humans were identified using Insilco screening. Incidentally factor XI or factor XIa were not identified as a target of asundexian by the approach used in this study, which leads to an interpretation that the potential cardiovascular benefits of asundexian by its action on other targets is likely. Based on the observations from this study, several such targets may account for the cardiovascular benefits of Asundexian.[4] One such target of interest was factor XII. Factor XI is reported to be contact activated by factor XII and also involving amplification loop by thrombin. Incidentally thrombin and factor XII were observed to be directly targeted by asundexian. Based on these observations it is suggested that the factor XI inhibition effect of asundexian is most likely an indirect effect coming from interfering with the factor XII and/or thrombin.

A very low rate of ischemic events were reported among patients receiving asundexian (50 mg/day) together with aspirin and P2Y12 inhibitor. This study identified an array of GPCR's, ion channels, kinases and enzymes as potential low affinity targets of asundexian. These relevant targets which can positively influence cardiovascular physiology are likely to be responsible for low rate of ischemic events observed following use of asundexian. The overall network pharmacology of asundexian reflects its potential cardiovascular beneficial effects and warrants this to be established in large scale randomised clinical trials.

ACKNOWLEDGEMENT

Research support from University College Dublin-Seed funding/Output Based Research Support Scheme (R19862, 2019), Royal Society-UK (IES\R2\181067, 2018) and Stemcology (STGY2708, 2020) is acknowledged.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

REFERENCES

1. Shoamanesh A, Mundl H, Smith EE, Masjuan J, Milanov I, Hirano T, *et al*. Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke (PACIFIC-Stroke): An international, randomised, double-blind, placebo-controlled, phase 2b trial. Lancet. 2022;400(10357):997-1007. doi: 10.1016/S0140-6736(22)01588-4, PMID 36063821.
2. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, *et al*. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): A multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022;399(10333):1383-90. doi: 10.1016/S0140-6736(22)00456-1, PMID 35385695.
3. Heitmeier S, Visser M, Tersteegen A, Dietze-Torres J, Glunz J, Gerdes C, *et al*. Pharmacological profile of asundexian, a novel, orally bioavailable inhibitor of factor XIa. J Thromb Haemost. 2022;20(6):1400-11. doi: 10.1111/jth.15700, PMID 35289054.
4. Rao SV, Kirsch B, Bhatt DL, Budaj A, Coppolecchia R, Eikelboom J, *et al*. A multicenter, Phase 2, randomized, placebo-controlled, double-blind, parallel-group, dose-finding trial of the oral Factor XIa inhibitor asundexian to prevent adverse cardiovascular outcomes following acute myocardial infarction. Circulation. 2022. doi: 10.1161/CIRCULATIONAHA.122.061612, PMID 36030390.
5. Manchukonda B, Kumar AH. Network profiling of hepatocellular carcinoma targets for evidence based pharmacological approach to improve clinical efficacy. BEMS Reports. 2022;8(1):11-5. doi: 10.5530/bems.8.1.4.
6. Kumar AH. Network pharmacology analysis of orally bioavailable SARS-CoV-2 protease inhibitor shows synergistic targets to improve clinical efficacy. BEMS Reports. 2021;7(2):21-4. doi: 10.5530/bems.7.2.8.

Cite this article : Kumar AHS. Pharmacological Targets of Asundexian Relevant to its Therapeutic Efficacy in Treating Cardiovascular Diseases. BEMS Reports. 2022;8(2):24-7.