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FULL PAPER

The effect of Atorvastatin on chronic subdural hematoma status: A systematic review of drug therapy

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Atorvastatin (ATO) with its chemical formula of (C33H35FN2O5) is one of the cholesterol-lowering drugs that can also reduce hematoma volume (HV). Considering the importance of pharmacological treatments in improving the patient condition, the aim of this study was to evaluate the ATO effect on chronic subdural hematoma (CSDH) status. In this systematic review (SR) study, all articles about the ATO effect on CSDH status were entered into a study, without time constraints, by two authors who were professional in SR articles. In the initial search, 176 articles were found, of which 73 articles were deleted due to duplicate records, and after further review and removal of unrelated articles, this number reduced to 11 articles, and systematic review data was reported with 11 articles. In all articles, radiological clinical findings were used to diagnose hematoma. In most of the reviewed articles, atorvastatin was effective in reducing subdural hemorrhage. The articles ranged from 2014 to 2021, the total sample size was 1278 patients and the follow-up period varied from 2 months to 4 years. Concerning the ATO effect in reducing HV status in CSDH patients, it is recommended to prescribe this drug to improve HV levels.

KEYWORDS

Atorvastatin; chronic subdural hematoma; systematic review.

Introduction

Atorvastatin (ATO) has the chemical formula of ($C_{33}H_{35}FN_2O_5$) and chemical structure displayed in Figure 1, belongs to the subgroup of statins. ATO is the most widely used statin drug that lowers plasma lipoprotein and cholesterol levels. Statins are cholesterol-lowering drugs due to 3-hydroxy-3-methylglutaryl-CoA reductase, which inhibits cholesterol biosynthesis in the liver [1]. The ATO properties can be examined in terms of pharmacokinetic, in relation to solubility with lipophilic properties, in relation to the food effect with reduced bioavailability, 98% with protein binding (%), in relation to CYP450 metabolism, isoenzyme with 3A4 and renal excretion (%) was less than 5. ATO is responsible for the cholesterol synthesis and prevents the production of mevalonic acid [2].

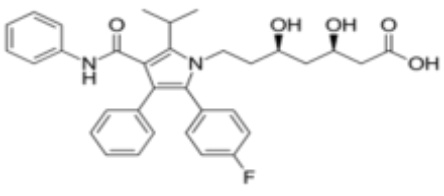

FIGURE 1 Chemical backbone of atorvastatin

ATO is one of the cholesterol-lowering drugs that can also reduce hematoma volume (HV) [3]. It has been used to reduce cholesterol and other types of fats and also plays an effective and beneficial role in improving laboratory parameters in chronic patients [4-6]. If a suitable and practical drug is used to improve patients' laboratory parameters, on the one hand, it can help improve the patient's condition, and on the other hand, it can decline many complications of the disease and additional treatment costs [3,7].

One of the types of injuries is head trauma, which is one of the most common reasons for referrals to the emergency department. In many cases, the patient needs emergency care and diagnostic tests should be requested upon referral and immediately after the clinical examination in most cases [8,9]. The head traumas may lead to various complications, such as subdural hematoma and epidural hematoma, both of which have many destructive effects on the clinical condition of patients. Identification of hematoma type can be effective in the source of bleeding, associated lesions, type of treatment, clinical course, and prognosis [10-12].

Subdural hematoma is one of the most problems related to neurological diseases, especially head trauma, which increases with age. In fact, this type of hematoma is considered as the most treatable cause of death and disability in traumatic brain injury patients, which can lead to increase intracranial pressure, neurological disorders, and loss of consciousness [13-15]. Other symptoms of these patients include dizziness, loss of consciousness, headache, and seizures, each of which, if not prevented or treated, can lead to more serious and dangerous complications [16].

To treat this complication, various surgical and pharmacological methods have been suggested. The goal of surgical treatment is to remove pressure from the brain hemisphere and prevent the recurrence of chronic subdural hematomas (cSDH) [17]. The surgical methods used to treat this disease may be invasive or less invasive, with less invasive methods having fewer complications. Among the surgical methods used to treat hematoma include skull perforation and hematoma drainage with or without catheter placement, closed perforation of the skull, drainage of the hematoma with an endoscope, and subdural-peritoneal (SP) shunting [18-20]. Pharmacological treatments include tranexamic acid [21,22], prednisolone [23], and atorvastatin [24,25].

Objectives

Considering the importance of pharmacological treatments in improving the patient condition, the aim of the present study was to evaluate the ATO effect on CSDH status.

Methods

According to PARISMA checklist [26], in this systematic review (SR) study, all articles about the ATO effect on CSDH status were included in a study, without time constraints, by two authors who were professional in SR articles. Persian and English keywords were used to the search process in domestic databases and only English keywords in the case of foreign databases using Google Scholar browser.

Inclusion criteria consisted of the availability of all articles entitled the ATO effect on CSHD in patients and the availability of studies in the human population. Exclusion criteria also included case-report and retracted articles or ones which had incomplete data.

Articles were evaluated using a checklist including questions about demographic variables (author name, year of publication, length of study period, and study population), study method (sample size, drug type and dose, and follow-up time), and also the research findings (the ATO effect on HV). Data were reported qualitatively using Excel 2007 software.

Results

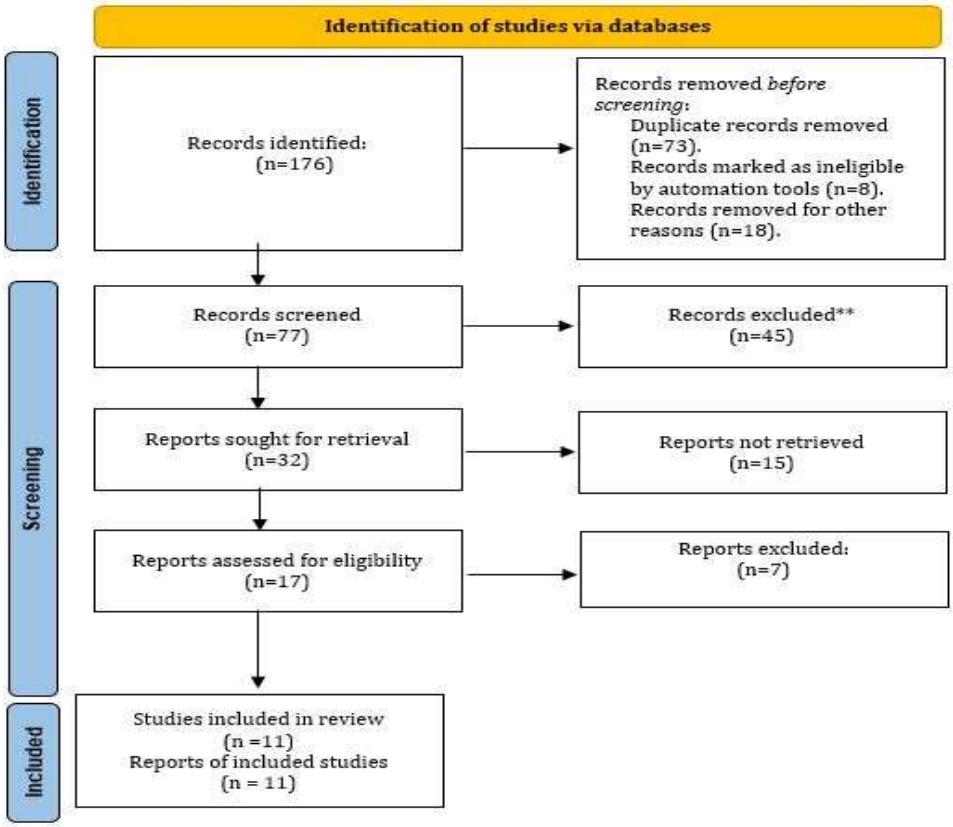

FIGURE 2 Flowcharts for systematic review

Study selection

In the initial search, 176 articles were found, of which 73 articles were deleted due to duplicate records, and after further review and removal of unrelated articles, this number reached 11 articles, and systematic review data was reported with 11 articles (Figure 2).

Measurement tools

In all articles, radiological clinical findings were used to diagnose hematoma.

Chronic subdural hematoma

In most of the reviewed articles, atorvastatin was effective in reducing subdural hemorrhage, while in the study of Wei *et al.* [27], this drug had no effect on reducing HV of the patients (Table 1).

Demographic status of articles

The articles ranged from 2014 to 2021, the total sample size was 1278 patients and the follow-up period varied from 2 months to 4 years.

TABLE 1 Status of reviewed articles

-	Author	Years	Duration of the study	Population	N	Age Mean (SD)	Intervention	Follow-up	Outcomes
1	Yang	2020(28)	2017-2018	Patients with diagnosis shock injury, fall, and traffic accident	E:28 C: 28	60.16(7.89)	E: oral ATO 20 mg	2 months	There was a significant reduction in HV level of the experimental group (P <0.008). The HV level was 20.1 (4.13) in the ATO group and 19.9 (4.42) in the C group before the intervention, which changed to 8.9 (3.24) in the ATO group, and 15.8 (3.98) in the C group after the intervention.
2	Sun	2021(29)	2019-2020	Elderly with surgical intervention	E: 21 C: 28	E:74.3 (7.3) C:74.6(7.4)	E: oral ATO	-	ATO could reduce CSDH in the elderly people of the experimental group compared with the control group in the postoperative stage.
3	Tang	2018(30)	2013-2016	undergoing burr-hole craniotomy	E: 125 C: 120	E: 63(3.3) C: 59.7(15.4)	E: oral ATO 20 mg (3 days postoperatively)	6 months	There was no difference between Group E and C in terms of mortality as well as postoperative complications. ATO use also reduced HV levels in patients, and this reduction in the experimental group was 12.55 Ml more than the control group.
4	Jiang	2018(31)	2014-2015	moderate or mild CH	E: 98 C: 98	E: 63(24) C: 67(26)	E: oral ATO 20 mg (8 weeks)	16 weeks	ATO had no significant effect on reducing the CSDH recurrence and the recurrence rate was 25 in the ATO group and 14 in the control group (P=0.50).
5	Wang	2021(32)	2013-2018	Patients with directional surgery YL-1 puncture needle	E: 301 C:215	E: 66.79(11.60) C: 67.52(11.94)	E: oral ATO 20 mg (1-3 months)	3 months	ATO had no significant effect on reducing the CSDH recurrence and the recurrence rate was 25 in the ATO group and 14 in the control group (P=0.50).
6	Wang	2020(33)	2014-2018	Patients over 18 years of age and diagnosed CSDH	E: 30 C: 30	E: 63.83(13.73) C: 69.37(10.9)	E: ATO 20 mg daily C: ATO+ dexamethasone	5 months	Concomitant use of ATO + dexamethasone has a greater effect in reducing the HV status of patients as compared to the ATO alone.
7	Wang	2014(34)	2010-2013	Patients with CSDH	E: 23 C: -	E: 67.87(14.87) C: -	E: oral ATO 20 mg (1-6 months)	3-36 months	ATO reduced HV levels from 48.70 ml to 16.64 ml. Hematoma was completely cured in 77.3% of patients.
8	David	2016(35)	2014	Patients with CSDH	E: 12 C: 12	E:78.3 (67-91)	E: ATO	6 months	ATO has very little effect on reducing HV levels.

9	Wei	2020(27)	1013-2018	burr-hole drainage at high altitudes	E: 43 C: 54	C: 79.5(58-95) E (No recurrence): 64.25(12.71) E (recurrence): 62.81(13.51) C (No recurrence): 60(13.66) C (recurrence): 61.14(16.36)	E: oral ATO 20 mg (3 months)	3 months	ATO had no effect on reducing HV levels. In the control group, the hematoma rate was 10.73 in patients with no recurrence and 10.27 in patients with recurrence of the control group. It was also 12.61 and 12.32 in the experimental group patients with no recurrence and recurrence patients, respectively.
10	QUAN	2020(36)	2016-2019	Diabetes, Myelodysplastic Syndromes, Coronary Artery, Old Cerebral Infarction, transient Ischemic Attacks	12	>90 Years	E: oral ATO 20 mg (8 weeks) C: ATO+ dexamethasone	6 weeks to 4 years	HV levels were decreased in both ATO and ATO + dexamethasone groups.

Discussion

Interventions by the medical staff can improve the health of patients[43, 44]. Pharmacological and non-pharmacological interventions are effective in measures related to health promotion and can be a good guide for the treatment team [37,38]. The aim of the present study was to evaluate the effect of ATO on CSDH status. There have been many studies on the effect of drugs on CSDH status. In the present study, we initially compare the ATO effect on CSDH status in patients, and then discuss other HV-reducing drugs in CSDH patients.

According to the findings of most of the reviewed articles, ATO reduced HV levels in patients. Various review studies have been conducted in this field. In this regard, He et al. reviewed 6 articles on the ATO effect on CSDH status of 759 patients between 2016 and 2018. They found that ATO improves neurological function and reduces CSDH [25]. Similarly, Wang et al. reviewed 12 articles on the effect of drugs (dexamethasone, atorvastatin, Goreisan, and prednisolone) on the CSDH status between 2014 and 2021. They found that ATO and tranexamic acid drugs reduced HV levels [39]. In another SR study, Qiu *et al*. reviewed three articles on the ATO effect on CSDH status of 156 patients between 2014 and 2017. They reported that ATO can lead to a decrease in patients' HV level [40]. Results of this SR study, in which reviewed 10 articles between 2014 and 2022, also revealed ATO reduced HV levels in most articles, which is consistent with the results of the studies mentioned above.

Holl *et al*. also reviewed seven articles on effect of corticosteroids on CSDH status of 1119 patients between 2007 and 2019. According to the findings, corticosteroid drugs

reduced HV in CSDH patients [41]. Other relevant studies include the study by Yao et al. that reviewed five articles on dexamethasone effect on CSDH status between 2001 and 2015. They found that dexamethasone reduced HV status in CSDH patients [42]. The findings of the present study are consistent with other studies and show the effect of drug therapy on reducing HV status in CSDH patients.

Conclusion

Considering the ATO effect in reducing HV status in CSDH patients, it is recommended to prescribe this drug to improve HV levels.

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Footnotes

Authors' Contribution: MH and KK contributed to all stages of the study, including conceptualization, data collection, data analysis, and manuscript writing.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: All participants signed informed consent.

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HV: hematoma volume

PARISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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References

[1] M. Hamzeh, F. Talebpour Amiri, A. Karimpour Malekshah, S. Yaghubi Beklar, J. Hosseinimehr, *J. Mazandaran Univ. Med. Sci.*, **2017**, *27*, 1-11. [Pdf], [Google Scholar], [Publisher]
[2] M. Schachter, *Fundam. Clin. Pharmacol.*, **2005**, *19*, 117-125. [crossref], [Google Scholar], [Publisher]
[3] F. Balavandi, F. Neystani, Y. Jamshidbeigi, A. Mozafri, *Eurasian Chem. Commun*., **2022**, *4*, 894-899. [crossref], [Pdf], [Publisher]
[4] M.M. Ramezani, N. Heydarieh, M. Khoshsokhan, *J. Shahid Sadoughi Univ. Med. Sci.*, **2016**, *24*, 429-440. [Pdf], [Google Scholar], [Publisher]
[5] F. Mayyas, D. Baydoun, R. Ibdah, K. Ibrahim, *J. Cardiovasc. Pharmacol. Ther.*, **2018**, *23*, 216-225. [crossref], [Google Scholar], [Publisher]
[6] R. Werida, I. Khairat, N.F. Khedr, *Biomed. Pharmacother*., **2021**, *135*, 111179. [crossref], [Google Scholar], [Publisher]
[7] A.R. Anness, A. Baldo, D.R. Webb, A. Khalil, T.G. Robinson, H.A. Mousa, *Placenta*, **2021**, *107*, 51-58. [crossref], [Google Scholar], [Publisher]
[8] T. Koiso, M. Goto, T. Terakado, Y. Komatsu, Y. Matsumaru, E. Ishikawa, *Sci. Rep*., **2021**, *11*, 1-7. [crossref], [Google Scholar], [Publisher]
[9] Z. Abid, N. Kuppermann, D.J. Tancredi, P.S. Dayan, *Ann. Emerg. Med.,* **2021**, *78*, 321-330. [crossref], [Google Scholar], [Publisher]
[10] Y.F. Mustafa, N.T. Abdulaziz, *NeuroQuantology*, **2021**, *19*, 175-186. [crossref], [Google Scholar], [Publisher]
[11] J. Shen, X. Shao, Q. Wang, R. Ge, J. Zhang, *World Neurosurg.,* **2019**, *132*, e391-e398. [crossref], [Google Scholar], [Publisher]
[12] V.N. Nguyen, D. Wallace, S. Ajmera, O. Akinduro, L.J. Smith, K. Giles, B. Vaughn, P. Klimo Jr, **2020**, *86*, 281-287. [crossref], [Google Scholar], [Publisher]
[13] M. Bechstein, R. McDonough, J. Fiehler, U. Zanolini, H. Rai, A. Siddiqui, E. Shotar, A. Rouchaud, M. Goyal, S. Gellissen, *Clin. Neuroradiol.*, **2022**, 1-7. [crossref], [Google Scholar], [Publisher]
[14] R. McDonough, M. Bechstein, J. Fiehler, U. Zanolini, H. Rai, A. Siddiqui, E. Shotar, A. Rouchaud, K. Kallmes, M. Goyal, S. Gellissen,

Am. J. Neuroradiol., **2022**, 1-9. [crossref], [Google Scholar], [Publisher]
[15] A. Grozenski, J. Zadell, J. Kiel, M. Parsons, *Curr. sports Med. Rep.*, **2021**, *20*, 16-18. [crossref], [Google Scholar], [Publisher]
[16] A. Nouri, R. Gondar, K. Schaller, T. Meling, *Brain and Spine*, **2021**, *1*, 100300. [crossref], [Google Scholar], [Publisher]
[17] W. Liu, N.A. Bakker, R.J.M. Groen, *J. Neurosurg.*, **2014**, *121*, 665-673. [crossref], [Google Scholar], [Publisher]
[18] Y.F. Mustafa, M.K. Bashir, M.K. Oglah, R.R. Khalil, E.T. Mohammed, *NeuroQuantology*, **2021**, *19*, 129-138. [crossref], [Google Scholar], [Publisher]
[19] M. Aromatario, A. Torsello, S. D'Errico, G. Bertozzi, F. Sessa, L. Cipolloni, B. Baldari, *Medicina*, **2021**, *57*, 125. [crossref], [Google Scholar], [Publisher]
[20] N.A. Shlobin, J. Kedda, D. Wishart, R.M. Garcia, G. Rosseau, *J. Gerontol.: Series A*, **2021**, *76*, 1454-1462. [crossref], [Google Scholar], [Publisher]
[21] V. Suresh, S. Sharma, *J. Stroke Cerebrovasc. Dis.,* 2021, *30*. [crossref], [Google Scholar], [Publisher]
[22] R. Lodewijkx, S. Immenga, R. van den Berg, R. Post, L.G. Westerink, R.J. Nabuurs, Can, A., W.P. Vandertop, D. Verbaan, *Br. J. Neurosurg.*, **2021**, *35*, 564-569. [crossref], [Google Scholar], [Publisher]
[23] F.R. Poulsen, S. Munthe, M. Søe, B. Halle, *Clin. Neurol. Neurosurg.*, **2014**, *123*, 4-8. [crossref], [Google Scholar], [Publisher]
[24] D. Wang, C. Gao, X. Xu, T. Chen, Y. Tian, H. Wei, S. Zhang, W. Quan, Y. Wang, S. Yue, Z. Wang, *J. Neurosurg.,* **2020**, *134*, 235-243. [crossref], [Google Scholar], [Publisher]
[25] C. He, P. Xia, J. Xu, L. Chen, Q. Zhang, *Neurosurg. Rev.*, **2021**, *44*, 479-484. [crossref], [Google Scholar], [Publisher]
[26] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group, *Ann. Intern. Med.*, **2009**, *151*, 264-269. [crossref], [Google Scholar], [Publisher]
[27] Y.F. Mustafa, *Appl. Nanosci.*, **2021**. [crossref], [Google Scholar], [Publisher]
[28] K. Yang, M. Qiu, H. Zhao, Z. Liu, L. Zheng, *Indian J. Pharm. Sci.*, **2020**, 86-92. [crossref], [Google Scholar], [Publisher]
[29] T. Sun, Y. Yuan, K. Wu, C. You, J.W. Guan, *Eur. Rev. Med. Pharmacol. Sci.*, **2021**, *25*, 7211-7217. [Pdf], [Google Scholar], [Publisher]
[30] R. Tang, J. Shi, X. Li, Y. Zou, L. Wang, Y. Chen, R. Yan, B. Gao, H. Feng, *World Neurosurg.*, **2018**, *117*, e425-e429. [crossref], [Google Scholar], [Publisher]
[31] R. Jiang, S. Zhao, R. Wang, H. Feng, J. Zhang, X. Li, Y. Mao, X. Yuan, Z. Fei, Y. Zhao, X. Yu, *JAMA Neurol.*, **2018**, *75*, 1338-1346. [crossref], [Google Scholar], [Publisher]
[32] D. Wang, H. Wang, M. Xu, P. Chen, B. Yu, J. Wen, H. Zhang, W. Zeng, S. He, C. Wang, *Clin. Neurol. Neurosurg.*, **2021**, *202*, 106548. [crossref], [Google Scholar], [Publisher]
[33] D. Wang, C. Gao, X. Xu, T. Chen, Y. Tian, H. Wei, S. Zhang, W. Quan, Y. Wang, S. Yue, Z. Wang, P. Lei, C. Anderson, J. Dong, J. Zhang, R. Jiang, *J. Neurosurg.,* **2020**, *134*, 235-243. [crossref], [Google Scholar], [Publisher]
[34] D. Wang, T. Li, Y. Tian, S. Wang, C. Jin, H. Wei, W. Quan, J. Wang, J. Chen, J. Dong, R. Jiang, J. Zhang, *J. Neurol. Sci.,* **2014**, *336*, 237-242. [crossref], [Google Scholar], [Publisher]
[35] Mustafa Y., Mohammed E., Khalil R., *Egypt. J. Chem.,* **2021**, *64*, 4461-4468. [crossref], [Google Scholar], [Publisher]
[36] W. Quan, J. Yuan, X. Liu, P. Li, J. Huang, Z. Gong, C. Gao, H. Luo, T. Xiang, D. Wang, S. An, Y. Wei, J. Sun, Y. Zhang, Z. Wang, P. Lei, Q. Deng, J. Zhang, R. Jiang, *Authorea Preprints,* 2020. [crossref], [Google Scholar], [Publisher]
[37] M. Motaghi, M. Borji, M. Moradi, *Biomed. Pharmacol. J.*, **2017**, *10*, 159-164. [crossref], [Google Scholar], [Publisher]
[38] B. Kazeminezhad, H. Taghinejad, M. Borji, A. Tarjoman, *J. Compr. Ped.*, **2018**, *9*, e62661. [crossref], [Google Scholar], [Publisher]
[39] X. Wang, J. Song, Q. He, C. You, *Front. Aging Neurosci.,* **2021**, *13*, 312. [crossref], [Google Scholar], [Publisher]
[40] Y.F. Mustafa, N.A. Mohammed, *Biochem. Cell. Arch.*, **2021**, *21*, 1991-1999. [Google Scholar], [Publisher]

[41] D.C. Holl, V. Volovici, C.M. Dirven, F., Miah I.P. Van Kooten, K. Jellema, W.C. Peul, N.A. van der Gaag, K.H. Kho, H.M. den Hertog, R. Dammers, H.F. Lingsma, *Acta Neurochir,* **2019**, *161*, 1231-1242. [crossref], [Google Scholar], [Publisher]
[42] Z. Yao, X. Hu, L. Ma, C. You, *Acta Neurochir*, **2017**, *159*, 2037-2044. [crossref], [Google Scholar], [Publisher]
[43] M. Azizi, A. Azadi, M. Otaghi, *The aging male*, **2020**, *23*, 687–693. [crossref], [Google Scholar], [Publisher]
[44] M. Otaghi, F. Hasanvand, M. Mozafari, A. Khorshidi, Rev. Latinoam, *Hipertens*., **2019**, *14*, 284-289. [Google Scholar], [Publisher]

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