



REVIEW ON EVALUATION OF FROZEN SHOULDER IN PEOPLE WITHDIABETES

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Abstract:

You may get a clinical diagnosis of frozen shoulder, which is a painful and debilitating illness. Classical clinical indications include painful restriction of shoulder motion due to persistent inflammation and proliferative fibrosis. Those with diabetes are at increased risk for developing the condition and may need surgical treatment more often. The practitioner managing diabetic frozen shoulder must find a middle ground between increasing the patients range of motion and alleviating discomfort and overtreating a disease that often resolves on its own. Physiotherapy and intra-articular injections are the mainstays of treatment, with hydro dilatation, anesthetic manipulation, and arthroscopic capsular release as potential next steps. In this study, we propose a care plan for treating patients with diabetic frozen shoulder based on a review of the current literature and correlation with experience at our hospital. Decisions on the patient's care should be made in collaboration with the patient, taking into account co-morbidities, severity, and the condition's natural history

Keywords: Management, Adhesive capsulitis, Frozen shoulder, Diabetes, Diabetic

INTRODUCTION

Frozen shoulder, or adhesive capsulitis, is a painful and disabling condition that affects the shoulder joint. It's easy to misdiagnose because of its telltale symptoms: discomfort with abrupt movement and a passivereduction of range of motion, especially in the shoulder's external rotation. Treatment of FS may be challenging; physicians frequently favor one or two therapy approaches based on patient variables and the severity of symptoms. To describe the data published to date, this literature review seeks to address the lack of current consensus in the treatment of diabetic FS[1][2].

Between 3% and 5% of the population has FS, however this number increases dramatically in diabetic individuals (up to 30%), who also tend to have more severe symptoms and be less responsive to therapy. Patients in the middle years are more likely to have this condition, and women are more likely than males to be affected by it. Besides being a result of injury, frozen shoulder is linked to conditions including Dupuytren's contracture, Peyronie's disease, and others that affect the connective tissue. Up to 11% of individuals having arthroscopy have suffered postoperative FS, with hyperglycemia being a Disabling pain is a common symptom reported by patients, although the underlying cause is not always apparent. Normal daily activities and abrupt motions may also trigger pain. If the patient's arm is shaken or dragged in any way, such as when the patient's kid tugs on their arm, the patient commonly reports a "sickening" pain. If you have this problem, you may have trouble sleeping on your afflicted side[6][5].

Visual examination of a patient with FS frequently reveals virtually nothing of note, other than any scarring or other remnants of past surgical intervention. Tenderness in the area of the anterior shoulder joint is another symptom that patients may experience along with worry or protectiveness over the affected limb. Less external rotational mobility characterizes the passive state. Since scapulothoracic motions may occasionally compensate and hide the diagnosis, isolating glenohumeral external rotation by retaining the scapula is essential. If discomfort and decreased range of motion are present, further investigation for rotator cuff disease, impingement, and other soft tissue abnormalities may be precluded[7][8]. predictor for this postoperative complication[3][4]

While the exact cause of FS is unknown, it is thought that chronic inflammation has a role in the development of proliferative fibrosis. On a macroscopic level, this manifests as a general thickening and congestion of the capsule, as well as an inflammatory look, most notably in the region of the rotator interval, the coracohumeral ligament, and the middle glenohumeral ligament. It has been seen microscopically that the damaged capsule has a greater number of fibroblasts, mast cells, macrophages, and T cells than the unaffected capsule. Increased levels of fibrotic growth factors, inflammatory cytokines, and interleukins are all linked to synovitis. Bunker found myofibroblast transformation, which is analogous to Dupuytren's disease of the hand[9][10][11].

A quicker rate of glycosylation has been proposed to



explain the greater prevalence of FS in people with diabetes mellitus, as well as other soft tissue illnesses including Dupuytren's disease. Increased levels of HBA1Care linked to the emergence of FS in people with diabetes. Diabetic synovial arthroscopic samples show elevated endothelial growth factors compared to non-diabetic FS and decreased inflammatory growth factors such as ADAMTS-4, MMP-1, and notably M-CSF. The latter may explain why the inflammatory response is diminished with time, which in turn makes the illness more severe and protracted. Yet, other research has shown no significant change in inflammatory markers between diabetes and non-diabetic people. It's important to remember that arthroscopic biopsies only represent a small fraction of the population with FS since they're only performed on the most severe and intractable cases. The course of FS is usually self-limiting, and it may be broken down into three phases: the freezing phase, in which pain and limited mobility are present, the frozen phase, in which stiffness predominates, and the thawing phase (symptoms resolve). In clinical settings, the stiffness vs pain dichotomy proposed by Hanchard et al. is more readily apparent. The normal progression of idiopathic FS is not usually seen in people with diabetes, and treatment is often necessary sooner rather than later[12][13]. Plain radiographs may be helpful in ruling out alternative causes of reduced passive and active range of motion, but otherwise imaging is not helpful in making a diagnosis of FS. Arthritis, a dislocated glenohumeral joint, and even bone tumors are among them. While magnetic resonance imaging (MRI) correlates with arthroscopic findings and may help with the diagnosis of FS, it is not often needed in the first examination until other intra-articular sources of pain, such as cuff or chondral disease, must be ruled out. Similarly, ultrasound sonography is only necessary if other concurrent shoulder diseases are suspected, although it might be deceiving if pain and stiffness hinder a complete examination[14].

METHODS

For this study, we searched PubMed for the phrases "diabetes" and "diabetic" in conjunction with "frozen shoulder" and "adhesive capsulitis," covering the time period of the previous 25 years, to conduct a systematic review of the English-language literature on the topic. Procedures for the systematic review are shown in Figure 1. Articles that were not written in English, did not deal with the treatment of diabetic frozen shoulder, dealt with outdated methods of care (such as open capsular release), or were reviews were not included in the analysis. After filtering for duplicates, the search returned 150 publications. Twenty-five main research publications providing

outcomes for the treatment of diabetic frozen shoulder were evaluated, and subsequent review articles, non-diabetic studies, and other unrelated articles were omitted. In Table 1 we provide the findings from the comprehensive review. Frozen shoulder is treated in a variety of ways, and it is generally agreed that the condition is self-limiting. Patients with diabetes (both type 1 and type 2) who have frozen shoulder often see their range of motion (ROM) return to normal on the unaffected side after an average of 9.7 years, regardless of whether they get therapy[15]. It is important to keep this in mind while interpreting the literature. Symptoms are managed with the goal of identifying and treating the persistent few[16][17].

Patients with diabetes in particular are prone to serious illness, usually requiring surgical intervention at an early stage. This means that in the case of diabetic FS, it is not always necessary to try less invasive measures before resorting to surgery.

The available literature on the treatment of diabetic FS is summarized in Table 1, where it is clear that there is no agreed-upon approach. Our systematic review yielded many noteworthy concerns that are easily identifiable (Table 1), underlining the challenges experienced by doctors in treating this severe and debilitating illness[18][19].

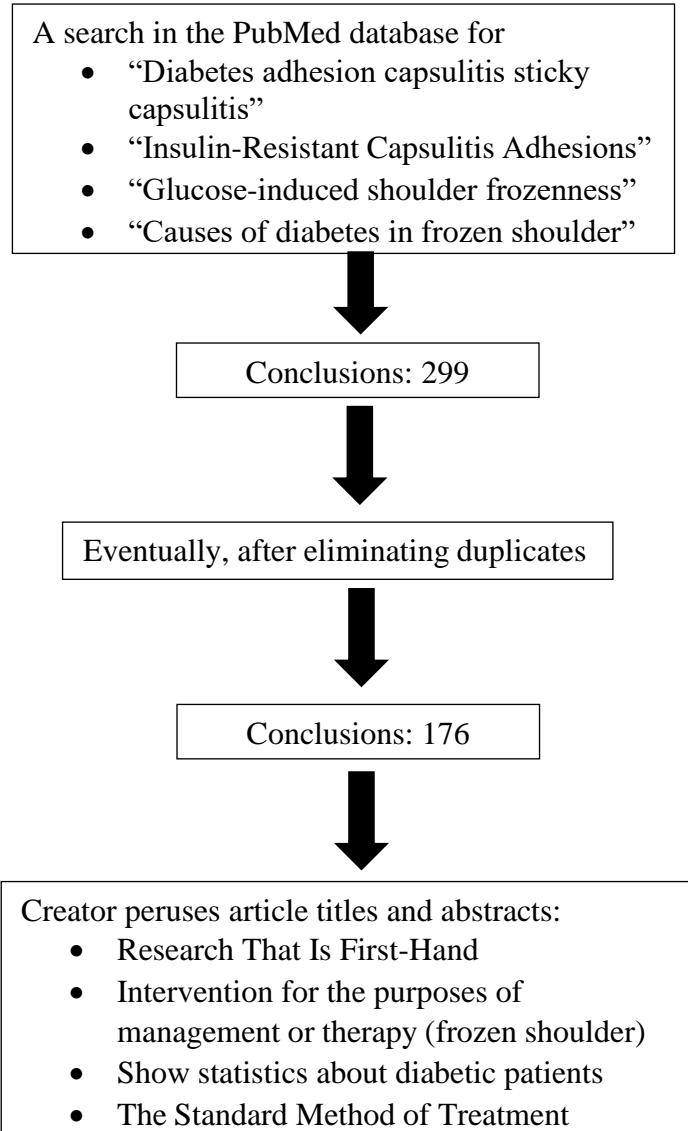


Table 1 contains a summary and analysis of 21 publications.

Excluded (n=139)

- Has nothing to do with frozen shoulder
- Diabetics: No Observable Consequences
- Evaluative Writings

Little randomized control trials and little high-quality data (level 2) exist for making management decisions

(RCTs). Improvements may be connected to the self-limiting character of diabetic FS, as shown by the RCTs



listed in Table 1 that concentrate on non-operative managements and compare physiotherapy regimens or steroid treatment. Nonetheless, the vast majority of the summarized data highlight the advantages of surgical intervention or hydrodilatation in diabetic patients.

More intensive therapy seems to be warranted, given that diabetic frozen shoulder is more severe and lasts longer. The remaining study publications all extol the virtues of the favored treatment technique, although with data based on relatively tiny sample sizes. Despite the lack of agreement on the most effective treatment for diabetic FS, there is agreement on how to gauge success. Almost all of the publications included in Table 1 provide measures of effectiveness, such as outcome ratings, range of motion, and pain intensity. Pain rating on a visual analog scale, the Oxford Shoulder Score, the Constant Shoulder Score, and the Disability Arm, Shoulder, and Hand Scores seem to be the most common outcome assessments. There is a clear need for more well-designed randomized trials due to the wide variety of therapies examined, the conflicting findings found in different articles, and the small sample sizes reported therein. Hydrodilatation as a non-surgical treatment option and hemoglobin A1c (or its equivalent) levels as a measure of glucose regulation should be included in this comparison of operative and non-operative treatments. The existing information makes it challenging for the doctor to determine the best way to treat diabetic FS. The table of findings from our systematic analysis provides an overview of both non-surgical and surgery treatment options for diabetic frozen shoulder, which we summarize and connect to our unit's approach to care below. For treating idiopathic FS, physiotherapy is often the first line of defense because of its proven efficacy in reducing symptoms and increasing function. Several studies show advantages with increased outcome ratings when PT is used to treat diabetic FS. Diabetic individuals have shown improvement over time in studies by Ekim et al. and Düzgün et al., with Düzgün et al. showing no significant difference to idiopathic FS. Two trials reported a final follow-up at 12 weeks and 8 weeks, respectively; the latter time point is unclear in the original paper, although most instances of frozen shoulder resolve with time. Nonetheless, poor glycemic control has been linked to an increased risk of FS in diabetic patients, which may explain why these individuals are more likely to need surgery. The results of these studies need to be confirmed in future research. Group physiotherapy sessions, passive exercises, and mild pendular exercises that don't push the patient too far above their pain threshold were shown to have the best results. Physiotherapy is widely recognized as an effective firstline of defense and as a

complementary therapeutic modality, especially for diabetes patients. Evidence suggests that oral anti-inflammatory drugs may enhance results similarly to intra-articular steroid injection whether used in combination with other treatment approaches or alone. Nevertheless, in diseases related to diabetes, it is important to evaluate the potential for systemic adverse effects from these drugs. Similarly, when taken orally, corticosteroids might have negative effects [20].

In idiopathic FS, intra-articular corticosteroid injections are often used to alleviate symptoms and hasten recovery. As compared to oral steroid therapy, intra-articular injections have a quicker onset and less systemic adverse effects. Diabetic individuals receiving intra-articular corticosteroid injections should be cautioned about the potential for elevated blood glucose levels for up to 7 days after the operation. Short-term pain alleviation and range of motion may be enhanced by intra-articular steroid injections, but these benefits are temporary. Hydrodilatation is a procedure in which a significant volume of normal saline is injected into the joint after a local anesthetic has been injected into the joint using ultrasound guidance in order to extend the capsular contractions. It is extensively used as an alternative to surgical surgery, and there is evidence to support its use in idiopathic frozen shoulder. There is evidence to show that diabetic individuals had a greater risk of conversion to arthroscopic release (20%) and recurrent hydrodilatation (50%) compared to idiopathic patients, despite published findings suggesting identical results to non-diabetic patients.

The first course of treatment for idiopathic FS at our clinic consists of intra-articular steroid injection and non-invasive physiotherapy. If the symptoms don't improve, hydrodilatation is the next step, followed by surgery if the stiffness is severe. With diabetic patients, we explore surgical intervention as an early therapeutic option and have a lower threshold to move to surgery than with hydrodilatation. Patients with diabetes are more likely to eventually need surgical intervention. In the treatment of idiopathic FS, manipulation under anesthesia (MUA) has demonstrated to produce excellent long-term improvements in outcome ratings regardless of symptom duration. Although Wang et al. found no significant differences between diabetic and non-diabetic individuals, Hamdan and Al-Essa found that MUA was related with worse outcomes for diabetes patients.

Recurrence of FS is more common in diabetic individuals after MUA, necessitating a second surgery (39%), and conversion to arthroscopic release (40%), especially in patients with type 1 diabetes (40%). The ideal time for MUA treatment



seemsto be between 7 and 10 months following the beginning of symptoms.

Due to the high rate of complication (30-40%) and the potential for iatrogenic fracture, as well as intra-articular, labral, and rotator cuff damage during MUA, our unit does not recommend MUA alone for the treatment of FS in diabetic patients and instead recommends arthroscopic capsular release followed by manipulation.

Range of motion and symptoms in idiopathic FS have been demonstrated to improve with arthroscopic capsularrelease in the short term (2, 8, 16, 32 weeks) and in the long term (7 years). Although arthroscopic release is less invasive than MUA, it is increasingly being utilized to treat chronic cases and those at high risk of recurrence, such as diabetic individuals.

There is little need for a second procedure after an arthroscopic release, and complications are uncommon. Patients with diabetes fared no worse than those without diabetes 7 months following arthroscopic release and MUA, according to a research by Bidwai et al. While Cho et al. found no difference in outcomes at ultimate follow-up (48 months), they did find worse results at 12 months in the diabetes group after arthroscopic release.

Although arthroscopic release has been shown to enhance outcome ratings, it has been shown to have a smaller effect on diabetes patients and to result in poor range of motion at final follow-up compared to non-diabetic individuals in other trials. Moreover, pre-operative intra-articular steroid injections may aid in enhancing the success of arthroscopic release.

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RESULTS

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arthroscopic release.

CONCLUSION

Maintaining the patient's range of motion and relieving their discomfort are two of the biggest challenges in treating diabetic frozen shoulder, despite the fact that the illness is self-limiting. Frozen shoulder is more common in those with diabetes and tends to be more severe and difficult to treat in those who already have it. While considering treatment options, physiotherapy should always be the first one recommended. There is no agreement on the optimal course of therapy, although taking into account the condition's natural history is essential before settling on one. Eventually, the treatment method will be determined by the patient's comorbidities, the severity of their condition, and their input. In our clinic, we often treat diabetic patients with frozen shoulder with intra-articular steroid injections and physical therapy if they appear in the early stages, and with surgical release if they show later with significant stiffness or fail conservative methods. The literature mainly supports this management approach; however, further well-designed randomized control studies are needed to compare surgery and non-operative approaches and explore the impact of diabetes control.



Study Techniques by Year	Degree of Proof	Full-record patients	Management	Evaluation of Results	Implications for Diabetic Frozen Shoulder Treatment
2015 Medical Research	5	35 (14 diabetic)	Capsulotomy (also known as arthroscopic capsular release) with or without a steroid injection before surgery.	CD-ROM, Bruin	When administered before to surgery, steroids reduce discomfort both during and after the procedure.
Repeated Case Studies from 2015	5	50	Incision and release of the articular capsule	Formats: CSS, ROM	Once the interventions were implemented, the outcomes significantly improved. All diabetics in the lower improvement group
Analysis of prior research from 2016	4	39 (18 diabetic)	Incision and release of the articular capsule	VAS, Range of Motion, UCLA, American Shoulder and Elbow Score	There were no significant differences in the end follow-up (48 months), however the DM group had worse results at 12 months.
2016 RCT	3	We have 41 diabetics in our midst.	A comparison of traditional physiotherapy (n = 23) and continuous both of which included electrotherapy	SPADI, VAS and CSS	After 4 and 12 weeks, both types of physiotherapy increased results. but was deemed to be more effective.
No-control prospective research conducted in 2016	3	53 (18 diabetic)	Capsular release and MUA via an arthroscopy	ROM, OSS	After 6-12 months, there was a significant improvement in ROM and OSS, and there were no problems, further surgeries, or recurrences. There's no distinction between diabetics and non-diabetics.
2017 Preliminary Study without a Control Group	3	52 (all diabetic)	Shockwave treatment used externally to the body (ESWT)	VAS, CSS and DASH	Outcome measures improved with once-weekly EWST for 3 weeks, however there was no comparison group.
2017 Predictive Analysis	3	729 (123 repeat)	Constant and primary use MUA	OSS, ROM	Type 1 diabetics are twice as likely to need a repeat MUA than the general population FS (60% vs. 23%), however there is no such difference with type 2 diabetics (0% vs. 0%). Recurrent MUA has a low risk of complications (0.2%).
Instances from 2017	5	119	<u>Hydrodilatation</u>	DASH, OSS	Lack of statistically significant improvement in symptoms compared to non-diabetics

REFERENCES

1. Suji, G., and S. Sivakami. "Approaches to the treatment of diabetes mellitus: an overview." Cellular and molecular biology (Noisy-le-Grand, France) 49.4 (2003): 635-639.

2. Skyler, Jay S. "Diabetes mellitus: pathogenesis and treatment strategies." Journal of medicinal chemistry 47.17 (2004): 4113-4117.
 3. Tran, Ngan, Bao Pham, and Ly Le. "Bioactive



- compounds in anti-diabetic plants: From herbal medicine to modern drug discovery." *Biology* 9.9 (2020): 252.
4. Arulayan, Nirmala, et al. "A database for medicinal plants used in the treatment of diabetes and its secondary complications." *Bioinformatics* 2.1 (2007): 22.
 5. Laylani, Layla Abd-Al-Sattar Sadiq, Ali Najdet Nasret Coran, and Zuhair Shakor Mahmood. "Foretelling Diabetic Disease Using a Machine Learning Algorithms." 2022 International Conference for Advancement in Technology (ICONAT). IEEE, 2022.
 6. Riaz, Samreen, Manal Tariq, and Sara Aslam. "Association of serum protein levels in the diabetic patients with risk of cardiovascular disease and nephropathy in Pakistani population." *J Res DiabetesMetab* 4.1 (2018): 011-015.
 7. Rafiei, M., et al. "Ankle/Brachial Index As A Valid Predictive Test For Detection Of Peripheral Arterial Disease, To Foretell The Possibility Of Ischemic Heart Diseases In Diabetic Patients." *Tehran University of Medical Sciences Journal* 62.3 (2004): 194-203.
 8. Gouveia, Luiza AG, et al. "Association between waist circumference (WC) values and hypertension, heart disease (HD) and diabetes, reported by the elderly-SABE survey: Health, wellness and aging, 2000 and 2006." *Archives of gerontology and geriatrics* 59.1 (2014): 62-68.
 9. Alkaragole, Mohammed Layth Zubairi, and Sefer Kurnaz. "Comparison of data mining techniques for predicting diabetes or prediabetes by risk factors." *International Journal of Computer Science and Mobile Computing* 8 (2019): 61-71.
 10. Mahmud, Ishtiaq, et al. "Hyperphosphataemia is associated with the diabetes-related cardiovascular risk factors." *Journal of Oleo Science* 60.2 (2011): 79-85. Marks, S. M. "Diabetes and tuberculosis, US National Health Interview Survey, 2000-2005." *The International journal of tuberculosis and lung disease* 15.7 (2011): 982-984.
 11. Manjrekar, Poornima Ajay, et al. "Fructosamine in Non-diabetic First Degree Relatives of Type 2 Diabetes Patients: Risk Assessor." *Journal of Clinical & Diagnostic Research* 6.5 (2012).
 12. Priyadarshinee, Sudipta, and Madhumita Panda. "Machine Learning Algorithms for Diabetes Prediction." *Innovations in Intelligent Computing and Communication: First International Conference, ICIICC 2022, Bhubaneswar, Odisha, India, December 16-17, 2022, Proceedings*. Cham: Springer International Publishing, 2023.
 13. RAFIEI, M., et al. "ANKLE/BRACHIAL INDEX AS A PREDICTOR OF CORONARY ARTERY DISEASES IN DIABETIC PATIENTS: WHAT IS THE BEST CUTOFF POINT?." *Iranian Heart Journal* 4.3 (2003): 47-55.
 14. Shareef, Asaad. Heart disease diagnostic using data mining techniques. MS thesis. Altınbaş Üniversitesi, 2018.
 15. Williams, Desmond E., et al. "Prevalence of impaired fasting glucose and its relationship with cardiovascular disease risk factors in US adolescents, 1999-2000." *Pediatrics* 116.5 (2005): 1122-1126.
 16. Elabasiry, Magdy, Sherif S. Hassan, and Safaa M. Altohamy. "Expression of cytokeratin 17 in normal and diabetic submandibular salivary gland (histological and immunohistochemical study)." *Tanta Dental Journal* 15.4 (2018): 241.
 18. Trelewicz, P., et al. "Activity of sodium-lithium cotransport in erythrocytes of patients with diabetes mellitus type I (IDDM) complicated by diabetic nephropathy in the renal failure stage." *Polskie Archiwum Medycyny Wewnetrznej* 97.6 (1997): 527-533.
 19. Christakis, Nicholas A. *Death foretold: prophecy and prognosis in medical care*. University of Chicago Press, 2001.
 20. Mitka, Mike. "Groups call truce over metabolic syndrome." *JAMA* 296.6 (2006): 641-641.
 21. Li, Q.; Qiu, L.; Tan, W.; Gu, G.; Guo, Z. Novel 1,2,3-triazolium-functionalized inulin derivatives: Synthesis, free radical-scavenging activity, and antifungal activity. *RSC Adv.* 2017, 7, 42225-42232.
 22. Tan, W.; Li, Q.; Dong, F.; Qiu, S.; Zhang, J.; Guo, Z. Novel 1,2,3-triazolium-functionalized starch derivatives: Synthesis, characterization, and evaluation of antifungal property. *Carbohydr. Polym.* 2017, 160, 163-171.
 23. Tan, W.; Li, Q.; Gao, Z.; Qiu, S.; Dong, F.; Guo, Z. Design, synthesis of novel starch derivative bearing 1,2,3-triazolium and pyridinium and evaluation of its antifungal activity. *Carbohydr. Polym.* 2017, 157, 236-243.
 24. Tan, W.; Zhang, J.; Luan, F.; Wei, L.; Li, Q.; Dong, F.; Guo, Z. Synthesis, characterization, and antifungal evaluation of novel 1,2,3-triazolium-functionalized starch derivative. *Int. J. Biol. Macromol.* 2017, 101, 845-851.
 25. Tan, W.; Li, Q.; Dong, F.; Zhang, J.; Luan, F.;



- Wei, L.; Chen, Y.; Guo, Z. Novel cationic chitosan derivative bearing 1,2,3-triazolium and pyridinium: Synthesis, characterization, and antifungal property. *Carbohydr. Polym.* 2018, 182, 180–187.
26. Steiner, I.; Stojanovic, N.; Bolje, A.; Brozovic, A.; Polancec, D.; Ambriovic-Ristov, A.; Stojkovic, M.R.; Piantanida, I.; Eljuga, D.; Kosmrlj, J.; et al. Discovery of 'click' 1,2,3-triazolium salts as potential anticancer drugs. *Radiol. Oncol.* 2016, 50, 280–288.
27. Rokitskaya, T.I.; Khailova, L.S.; Makarenkov, A.V.; Shunaev, A.V.; Tatarskiy, V.V.; Shtil, A.A.; Ol'shevskaya, V.A.; Antonenko, Y.N. Carborane derivatives of 1,2,3-triazole depolarize mitochondria by transferring protons through the lipid part of membranes. *Biochim. Biophys. Acta Biomembr.* 2019, 1861, 573–583.
28. Almeida, A.C.; Meinel, R.S.; Leal, Y.L.; Silva, T.P.; Glanzmann, N.; Mendonca, D.V.C.; Perin, L.; Cunha-Júnior, E.F.; Coelho, E.A.F.; Melo, R.C.N.; et al. Functionalized 1,2,3-triazolium salts as potential agents against visceral leishmaniasis. *Parasitol. Res.* 2022, 121, 1389–1406.
29. Fletcher, J.T.; Sobczyk, J.M.; Gwazdac, S.C.; Blanck, A.J. Antimicrobial 1,3,4-trisubstituted-1,2,3-triazolium salts. *Bioorg. Med. Chem. Lett.* 2018, 28, 3320–3323.
30. Godard, J.; Gibbons, D.; Leroy-Lhez, S.; Williams, R.M.; Villandier, N.; Ouk, T.S.; Brégier, F.; Sol, V. Development of phenalenonetriazolium salt derivatives for aPDT: Synthesis and antibacterial screening. *Antibiotics* 2021, 10, 626. Subedi, Y.P.; Alfindee, M.N.; Shrestha, J.P.; Chang, C.T. Tuning the biological activity of cationic anthraquinone analogues specifically toward *Staphylococcus aureus*. *Eur. J. Med. Chem.* 2018, 157, 683–690. [CrossRef]
31. Subedi, Y.P.; Chang, C.T. Cationic anthraquinone analogs as selective antimicrobials. *Microbiol. Insights* 2019, 12, 1178636119847809.
32. Shyam, R.; Forestier, C.; Charbonnel, N.; Roy, 43. substituted 1,2,3-triazoles and related bistriazoles. *Org. Lett.* 2016, 18, 2511–2514.
44. Huisgen, R. 1,3-Dipolar Cycloadditions. Past and Future. *Angew. Chem. Int. Ed.* 1963, 2, 565–598.
45. Rostovtsev, V.V.; Green, L.G.; Fokin, V.V.; Sharpless, K.B. A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem. Int. Ed.* 2002, 41, 14.
46. Purnell, L.G.; Shepherd, J.C.; Hodgson, D.J. O.; Taillefumier, C.; Faure, S. Solution-phase synthesis of backbone-constrained cationic peptoid hexamers with antibacterial and anti-biofilm activities. *Eur. J. Org. Chem.* 2021, 2021, 5813–5822. [CrossRef]
33. Yoshimura, Y.; Tomimatsu, K.; Nishimura, T.; Miyake, A.; Hashimoto, N. Studies on condensed-heterocyclicazolium cephalosporins.
34. V. Synthesis and antibacterial activity of 3-(condensed-triazolo-pyridinium, -pyrimidinium, and -pyridazinium)-methyl cephalosporins. *J. Antibiot.* 1992, 45, 721–734.
35. Wilson, J.A.; Lin, Z.J.; Rodriguez, I.; Ta, T.; Martz, L.; Fico, D.; Johnson, S.S.; Gorden, J.D.; Shelton, K.L.; King, L.B. Synthesis, characterization, and antimicrobial activity of lipophilic N,N'-bis-substituted triazolium salts. *J. Heterocycl. Chem.* 2021, 59, 577–587.
36. Peiteado, Z.M. Synthesis, Applications and Reactivity of 1,2,3-Triazolium Salts. Ph.D. Thesis, University of the Basque CountryUPV/EHU, Bilbao, Spain, 2015.
37. Yacob, Z.; Liebscher, J. Chemistry of 1,2,3-triazolium salts. In *Chemistry of 1,2,3-Triazoles*; Dehaen, W., Bakulev, V.A., Eds.; Springer International Publishing: Cham, Germany, 2015; Volume 40, pp. 167–210.
38. Huang, D.; Zhao, P.; Astruc, D. Catalysis by 1,2,3-triazole- and related transition-metal complexes. *Coord. Chem. Rev.* 2014, 272, 145–165.
39. Mishra, R.; Mishra, J.S.; Chaubey, S.A. Recent advances on triazolium ionic liquids: Synthesis and applications. *Curr. Org. Chem.* 2019, 23, 1239–1255.
40. Kolb, H.C.; Finn, M.G.; Sharpless, K.B. Click chemistry: Diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed.* 2001, 40, 2004–2021.
41. Maity, R.; Sarkar, B. Chemistry of compounds based on 1,2,3-triazolylidene-type mesoionic carbenes. *J. Am. Chem. Soc.* 2022, 144, 22–57
42. Monasterio, Z.; Irastorza, A.; Miranda, J.I.; Aizpurua, J.M. Site-selective N-dealkylation of 1,2,3-triazolium salts: A metal-free route to 1,5-Interaction of metal ions with 8-azapurines. synthesis and structure of tetrachlorobis-2[(5-amino-4-carboxamidinium)[1,2,3]triazole]copper(II) monohydrate. *J. Am. Chem. Soc.* 1974, 97, 9–13. [CrossRef] *Int. J. Mol. Sci.* 2023, 24, 10694 19 of 19
48. Ma, J.; Ding, S. Transition metal-catalyzed cycloaddition of azides with internal alkynes. *Asian J. Org. Chem.* 2020, 9, 1872–1888.
49. Boren, B.C.; Narayan, S.; Rasmussen, L.K.;



- Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V.V. Ruthenium-catalyzed azide-alkyne cycloaddition: Scope and mechanism. *J. Am. Chem. Soc.* 2008, 130, 8923–8930.
50. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62: 10–29.
51. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144: 646–74.
52. Duffy MJ. The war on cancer: are we winning? *Tumour Biol* 2013; 34: 1275–84.
53. Kolb HC, Sharpless KB. The growing impact of click chemistry on drug discovery. *Drug Discov Today* 2003; 8: 1128–37.
54. Košmrlj J. *Click Triazoles*, 1 edn, vol. 28. Berlin Heidelberg: Springer-Verlag; 2012.
55. Aizpurua JM, Fratila RM, Monasterio Z, Perez-Esnaola N, Andreieff E, Irastorza A, et al. Triazolium cations: from the “click” pool to multipurpose applications. *New J Chem* 2014; 38: 474–80.
56. Massarotti A, Aprile S, Mercalli V, Del Grosso E, Grosa G, Sorba G, et al. Are 1,4-and 1,5-disubstituted 1,2,3-triazoles good pharmacophoric groups? *Chem Med Chem* 2014; 9: 2497–508.
- da Silva EN, Jr., Cavalcanti BC, Guimaraes TT, Pinto Mdo C, Cabral IO, Pessoa C, et al. Synthesis and evaluation of quinonoid compounds against tumor cell lines. *Eur J Med Chem* 2011; 46: 399–410.
- Ahmed N, Konduru NK, Ahmad S, Owais M. Design, synthesis and antiproliferative activity of functionalized flavone-triazole-tetrahydropyran conjugates against human cancer cell lines. *Eur J Med Chem* 2014; 82: 552–64.
57. Souza-Fagundes, E.M.; Delp, J.; Prazeres, P.D.M.; Marques, L.B.; Carmo, A.M.L.; Stroppa, P.H.F.; Glanzmann, N.; Kisitu, J.; Szamosvari, D.; Böttcher, T.; et al. Correlation of structural features of novel 1,2,3-triazoles with their neurotoxic and tumoricidal properties. *Chem. Biol. Interact.* 2018, 291, 253–263.
58. Ramos, J.P.; Abdel-Salam, M.A.L.; Nobre, D.A.B.; Glanzmann, N.; de Souza, C.P.; Leite, E.A.; de Abreu Teles, P.P.; Barbosa, A.S.; Barcelos, L.S.; Dos Reis, D.C.; et al. Acute toxicity and antitumor potential of 1,3,4-trisubstituted-1,2,3-triazole dhmtAc-loaded liposomes on a triple-negative breast cancer model. *Arch. Pharm.* 2022, 355, e2200004.
59. Shrestha, J.P.; Chang, C.W. Safe and easy route for the synthesis of 1,3-dimethyl-1,2,3-triazolium salt and investigation of its anticancer activities. *Bioorg. Med. Chem. Lett.* 2013, 23, 5909–5911.
60. Shrestha, J.P.; Subedi, Y.P.; Chen, L.; Chang, C.W.T. A mode of action study of cationic anthraquinone analogs: A new class of highly potent anticancer agents. *MedChemComm* 2015, 6, 2012–2022.
62. Wang, R.; Li, Y.; Dehaen, W. Antiproliferative effect of mitochondria-targeting allobetulin 1,2,3-triazolium salt derivatives and their mechanism of inducing apoptosis of cancer cells. *Eur. J. Med. Chem.* 2020, 207, 112737.
63. Riela, S.; Massaro, M.; Colletti, C.G.; Bommarito, A.; Giordano, C.; Milioto, S.; Noto, R.; Poma, P.; Lazzara, G. Development and characterization of co-loaded curcumin/triazole-halloysite systems and evaluation of their potential anticancer activity. *Int. J. Pharm.* 2014, 475, 613–623.